Transsphenoidal Surgery

Complication Avoidance and Management Techniques

Edward R. Laws, Jr.
Aaron A. Cohen-Gadol
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Editors
Edward R. Laws, Jr.
Department of Neurosurgery
Harvard Medical School Brigham
and Women's Hospital
Boston, MA, USA

Theodore H. Schwartz
Department of Neurosurgery
Weill Cornell Medical College
New York Presbyterian Hospital
New York, NY, USA

Aaron A. Cohen-Gadol
Department of Neurosurgery
Indianapolis Methodist Hospital
Indianapolis, IN, USA

Jason P. Sheehan
Department of Neurological Surgery
University of Virginia
Charlottesville, VA, USA

Department of Radiation Oncology
University of Virginia
Charlottesville, VA, USA

Videos can also be accessed at http://link.springer.com/book/10.1007/978-3-319-56691-7

ISBN 978-3-319-56689-4 ISBN 978-3-319-56691-7 (eBook)
DOI 10.1007/978-3-319-56691-7

Library of Congress Control Number: 2017947772

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Over the past decade, there have been significant advances in the field of transsphenoidal surgery. Among the most notable is the steady advancement of this fundamental concept in approaching a variety of anterior skull base lesions. The advancements in this field have resulted from improved preoperative and intraoperative radiological imaging, enhanced microsurgical and endoscopic techniques, refinements in the delivery of ionizing radiation including stereotactic radiosurgery, a more thorough understanding of tumor biology, and development of medical approaches predicated on the underlying tumor biology. These are essential aspects of modern skull base surgery and have become a major focus of collegial interdisciplinary efforts.

The overall aim of the current work was to detail contemporary clinical knowledge and multidisciplinary approaches for management of patients harboring pituitary adenomas and other types of sellar and parasellar tumors. Many of the chapters focus on surgical techniques, and particular emphasis is placed not only on the advantages and disadvantages of a particular approach, but on methods to avoid complications. The anatomic complexities of the sellar and parasellar area make this one of the most challenging regions for delivering therapeutic interventions. Even the best devised therapeutic plans can at times fail and thereby necessitate that the successful clinician and surgeon must possess an exquisite understanding of complication recognition and management.

The book spans topics that range from the history of pituitary surgery and the transsphenoidal approach to the quality of life assessments, so important to our patients. Intervening chapters focus on preoperative assessment and planning, intraoperative techniques, postoperative management, and adjuvant therapy for those patients with recurrent or residual disease. The majority of the chapters contain illustrations which we believe the readers will find invaluable. The diversity of the topics also underscores the multidisciplinary team approach essential to successful management of this patient group.

Each chapter is written by widely recognized and established experts in the field. Importantly, the contributors share many "pearls" of wisdom gained over decades of clinical experience. It is from our patients that we learn and perfect the indications and limitations of our methods, and for that, we owe our patients tremendous gratitude and respect. We truly value the substantial contributions to the creation of this multiauthored work. The professional editorial efforts of Springer, including that of

project manager Kevin Wright, have been indispensable On a personal note, we wish to thank our families for their support throughout this project. They have demonstrated tremendous understanding of our time spent writing and editing this text. Without the help of so many, this project could not have been brought to fruition.

Charlottesville, VA, USA — Jason P. Sheehan
Indianapolis, IN, USA — Aaron A. Cohen-Gadol
New York, NY, USA — Theodore H. Schwartz
Boston, MA, USA — Edward R. Laws, Jr.

Contents

1 **Evolution of Pituitary Surgery and the Transsphenoidal Approach** 1
Luke Smith, Gautam U. Mehta, and Russell R. Lonser

2 **The History of Trans-sphenoidal Surgery for Pituitary Tumours** 11
James A.J. King and Andrew H. Kaye

3 **Principles and Pitfalls of Anesthesia for Transsphenoidal Surgery** 27
Lauren K. Dunn and Edward C. Nemergut

4 **Operative Indications and Pitfalls in Patient Selection for Surgery of Pituitary Tumors** 43
Chikezie Eseonu, Christina Jackson, and Alfredo Quinones-Hinojosa

5 **The Perioperative and Postoperative Care for Pituitary Patients** 59
Saira Khan and Roberto Salvatori

6 **Neuro-ophthalmology of Pituitary Tumors** 71
Robert M. Mallery and Sashank Prasad

7 **Rhinologic Evaluation of Patients Undergoing Transsphenoidal Surgery** 87
Michael Freeman, Jose Gurrola II, and Spencer C. Payne

8 **Imaging of the Sella and Parasellar Region** 95
Amar P. Patel, Vivek P. Patel, and Max Wintermark

9 **Classification, Pathobiology, Molecular Markers, and Intraoperative Pathology** 113
M. Beatriz S. Lopes

10 **Surgical Anatomy of the Sellar Region** 145
Nathan T. Zwagerman, Stefan Lieber, and Juan C. Fernandez-Miranda

11 Combined Hybrid Microscopic and Endoscopic Transsphenoidal Surgery: Anatomy, Instrumentation, and Technique 167
David S. Baskin and Robert A. Scranton

12 Transcranial Approaches to the Sellar and Parasellar Areas 191
Bradley N. Bohnstedt, Todd Eads, Jonathan Weyhenmeyer, and Aaron A. Cohen-Gadol

13 Endoscopic Transsphenoidal Surgery: Anatomy, Instrumentation, and Technique 213
Paolo Cappabianca, Luigi Maria Cavallo, Domenico Solari, and Alberto di Somma

14 Three-Dimensional Endoscopy for Skull Base Surgery 233
Jason K. Chu, Brandon A. Miller, and Nelson M. Oyesiku

15 Endoscopic Transsphenoidal Pituitary Surgery: Results and Complications 245
Harminder Singh, Walid I. Essayed, Ibrahim Hussain, Kryscilla Yang, Vijay K. Anand, and Theodore H. Schwartz

16 Intraoperative Imaging for Pituitary Surgery 259
Peter T. Sylvester and Michael R. Chicoine

17 The Role of Endoscopic Transsphenoidal Surgery in the Management of Complex Lesions Involving the Skull Base 277
James K. Liu, Eleonora F. Spinazzi, Jean Anderson Eloy, and William T. Couldwell

18 Closure Methods Following Transsphenoidal Surgery 303
Paul A. Gardner, Carl H. Snyderman, Juan C. Fernandez-Miranda, and Eric W. Wang

19 Complications with Transsphenoidal Surgery: A Review 315
Garni Barkhoudarian and Daniel F. Kelly

20 Rhinological Complications: Avoidance and Management 345
Gustavo J. Almodovar-Mercador, Theodore H. Schwartz, and Vijay K. Anand

21 Medical Management for Pituitary Adenoma Patients 359
Gregory K. Hong

22 Transsphenoidal Surgery for Recurrent Pituitary Disease 383
Joshua Bakhsheshian and Gabriel Zada

23 Transsphenoidal Surgery for Craniopharyngiomas 403
Kenneth Foxx, Stephen Sandwell, Howard Silberstein, G. Edward Vates, Matthew Miller, Ismat Shafiq, Ekaterina Manuylova, and Laura Calvi

24 Transsphenoidal Surgery for Cushing's Disease 427
Kalmon D. Post, Margaret Pain, Hekmat Zarzour, and Joshua Bederson

25 Transsphenoidal Surgery for Acromegaly 441
Edward R. Laws Jr., David J. Cote, and Sherry Iuliano

26 Transsphenoidal Surgery for Prolactinomas 457
Won Kim, Srinivas Chivukula, Anthony Heaney, Marilene Wang, and Marvin Bergsneider

27 Transsphenoidal Surgery for Nonfunctioning Pituitary Adenomas 471
Sarah T. Menacho and Ian E. McCutcheon

28 Pituitary Tumors in Pediatric Patients 487
Robert F. Dallapiazza and John A. Jane Jr.

29 Pituitary Apoplexy 499
Patrick M. Flanigan, Arman Jahangiri, Han S. Lee, and Manish K. Aghi

30 Anatomical Approaches to Giant Pituitary Tumors 517
André Beer-Furlan, Ralph Abi-Hachem, Ali O. Jamshidi, Ricardo L. Carrau, and Daniel M. Prevedello

31 Postoperative Management of Patients Following Transsphenoidal Surgery 531
Martin J. Rutkowski and Sandeep Kunwar

32 Stereotactic Radiosurgery for Pituitary Adenomas 539
Cheng-Chia Lee and Jason P. Sheehan

33 Radiation Therapy for Pituitary Tumors 559
Trevor J. Royce, Jay S. Loeffler, and Helen A. Shih

34 Cytotoxic Chemotherapy and Targeted Therapy for Aggressive Pituitary Tumors 581
Alissa A. Thomas and Camilo E. Fadul

35 Quality of Life in Patients with Pituitary Adenomas 595
Douglas A. Hardesty and Andrew S. Little

Index 611

Contributors

Ralph Abi-Hachem, MD The Ohio State University Wexner Medical Center, Department of Neurological Surgery, Columbus, OH, USA

Manish K. Aghi, MD, PhD Neurological Surgery, University of California at San Neurological Surgery Francisco, San Francisco, CA, USA

Vijay K. Anand, MD, FACS Department of Otolaryngology—Head and Neck Surgery, Weill Cornell Medical College, New York Presbyterian Hospital, Weill Medical College of Cornell University, New York, NY, USA

Joshua Bakhsheshian, MD, MS Department of Neurological Surgery, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Garni Barkhoudarian, MD Pacific Pituitary Disorders Center, John Wayne Cancer Institute at Providence Saint John's Health Center, Santa Monica, CA, USA

David S. Baskin, MD, FACS, FAANS Professor, Vice Chair, and Program Director, Department of Neurosurgery, Houston Methodist Institute, Houston, TX, USA

Director, Department of Neurosurgery, Kenneth R. Peak Brain and Pituitary Tumor Treatment Center, Houston Methodist Neurological Institute, Houston, TX, USA

Joshua Bederson, MD Department of Neurosurgery, Mount Sinai School of Medicine, New York, NY, USA

André Beer-Furlan, MD The Ohio State University Wexner Medical Center, Department of Neurological Surgery, Columbus, OH, USA

Marvin Bergsneider, MD Department of Neurosurgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Bradley N. Bohnstedt, MD Department of Neurosurgery, Oklahoma University Health Sciences Center, Oklahoma City, Oklahoma, USA

Laura M. Calvi, MD Department of Neurosurgery, University of Rochester Medical Center, Rochester, NY, USA

Paolo Cappabianca, MD Division of Neurosurgery, Department of Neurosciences, Reproductive and Odontostomatological Sciences, Università degli Studi di Napoli "Federico II", Naples, Italy

Ricardo L. Carrau, MD The Ohio State University Wexner Medical Center, Department of Neurological Surgery, Columbus, OH, USA

Luigi Maria Cavallo, MD, PhD Division of Neurosurgery, Department of Neurosciences, Reproductive and Odontostomatological Sciences, Università degli Studi di Napoli "Federico II", Naples, Italy

Michael R. Chicoine, MD Department of Neurological Surgery, Washington University School of Medicine, St. Louis, MO, USA

Srinivas Chivukula, MD Department of Neurosurgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Jason K. Chu, MD, MSc Department of Neurosurgery, Emory University, Atlanta, GA, USA

Aaron A. Cohen-Gadol, MD, MSc Department of Neurosurgery, Indianapolis Methodist Hospital, Indianapolis, IN, USA

William T. Couldwell, MD, PhD Department of Neurosurgery, University of Utah, Salt Lake City, UT, USA

David J. Cote, BS Department of Neurosurgery, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA

Robert F. Dallapiazza, MD, PhD Department of Neurosurgery, University of Virginia Health System, Charlottesville, VA, USA

Lauren K. Dunn, MD, PhD University of Virginia, Department of Anesthesiology, Charlottesville, VA, USA

Todd Eads, MD Department of Neurological Surgery, Goodman Campbell Brain and Spine, Indiana University, Indianapolis, Indiana, USA

Jean Anderson Eloy, MD Department of Neurological Surgery, Rutgers New Jersey Medical School, Newark, NJ, USA

Center for Skull Base and Pituitary Surgery, Neurological Institute of New Jersey, Rutgers New Jersey Medical School, Newark, NJ, USA

Department of Otolaryngology-Head & Neck Surgery, Rutgers New Jersey, New Jersey Medical School, Newark, NJ, USA

Department of Ophthalmology and Visual Science, Rutgers New Jersey Medical School, Newark, NJ, USA

Chikezie Eseonu, MD Johns Hopkins Hospital, Neurosurgery, Baltimore, MD, USA

Walid I. Essayed, MD Department of Neurosurgery, Brigham and Women's Hospital, Boston, MA, USA

Camilo E. Fadul, MD, FAAN Department of Neurology, University of Virginia, Charlottesville, VA, USA

Juan C. Fernandez-Miranda, MD Department of Neurological Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Patrick M. Flanigan, BS Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA

Kenneth Foxx, MD Neurosurgery Resident PGY-5, University of Rochester Medical Center, Rochester, NY, USA

Michael Freeman, BS University of Virginia School of Medicine, Charlottesville, VA, USA

Sarah T. Menacho, MD University of Texas MD Anderson Cancer Center, Department of Neurosurgery, Houston, TX, USA

Paul A. Gardner, MD Department of Neurological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Jose Gurrola II, MD Department of Otolaryngology, Head & Neck Surgery, University of Virginia School of Medicine, Charlottesville, VA, USA

Douglas A Hardesty, MD Department of Neurosurgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA

Anthony Heaney, MD, PhD Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Alfredo Quinones-Hinojosa, MD Mayo Clinic Neurosurgery, Jacksonville, FL, USA

Gregory K. Hong, MD, PhD Division of Endocrinology, Department of Medicine, University of Virginia Health System, Charlottesville, VA, USA

Ibrahim Hussain Department of Neurosurgery, Weill Cornell Medical College, New York Presbyterian Hospital, New York, NY, USA

Sherry Iuliano, MSN, NP-C Department of Neurosurgery, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA

Christina Jackson, MD Johns Hopkins Hospital, Neurosurgery, Baltimore, MD, USA

Arman Jahangiri, BS University of California at San Francisco, Neurological Surgery, San Francisco, CA, USA

Ali O. Jamshidi, MD The Ohio State University Wexner Medical Center, Department of Neurological Surgery, Columbus, OH, USA

John A. Jane Jr., MD Department of Neurosurgery, University of Virginia Health System, Charlottesville, VA, USA

Andrew H. Kaye Department of Neurosurgery, The Royal Melbourne Hospital, Melbourne, Australia

James A.J. King Department of Neurosurgery, The Royal Melbourne Hospital, Melbourne, Australia

Won Kim, MD Department of Neurosurgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Daniel F. Kelly, MD Pacific Pituitary Disorders Center, John Wayne Cancer Institute at Providence Saint John's Health Center, Santa Monica, CA, USA

Saira Khan, MD Division of Endocrinology, Department of Medicine, and Pituitary Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Sandeep Kunwar, MD California Center for Pituitary Disorders, Department of Neurological Surgery, University of California, San Francisco, CA, USA

Sarah T. Menacho, MD University of Utah, Department of Neurosurgery, Salt Lake City, UT, USA

Edward R. Laws, Jr., MD, FACS, FAANS Department of Neurosurgery, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA

Cheng-Chia Lee, MD Department of Neurosurgery, University of Virginia, Charlottesville, VA, USA

Han S. Lee, MD, PhD University of California at San Francisco, Neurological Surgery, San Francisco, CA, USA

Stefan Lieber, MD Department of Neurological Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Andrew S. Little, MD Department of Neurosurgery, Neuroscience Publications, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA

James K. Liu, MD Department of Neurological Surgery, Rutgers New Jersey Medical School, Newark, NJ, USA

Center for Skull Base and Pituitary Surgery, Neurological Institute of New Jersey, Rutgers New Jersey Medical School, Newark, NJ, USA

Department of Otolaryngology-Head & Neck Surgery, Rutgers New Jersey, New Jersey Medical School, Newark, NJ, USA

Jay S. Loeffler, MD Harvard Medical School, Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA

Russell R. Lonser, MD Department of Neurological Surgery, The Ohio State University Wexner Medical Center, Columbus, OH, USA

M. Beatriz S. Lopes, MD, PhD Department of Pathology, University of Virginia School of Medicine and Health System, Charlottesville, VA, USA

Ekaterina Manuylova, MD Department of Medicine, University of Rochester Medical Center, Rochester, NY, USA

Robert M. Mallery, MD Division of Neuro-Ophthalmology, Department of Neurology, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA

Ian E. McCutcheon, MD University of Texas, Anderson Cancer Center, Neurosurgery, Houston, TX, USA

Gustavo J. Almodovar-Mercador, MD Weill Cornell Medical College, New York Presbyterian Hospital, Weill Medical College of Cornell University, Otolaryngology—Head and Neck Surgery, New York, NY, USA

Matthew Miller, MD, FACS Department of Otolaryngology, University of Rochester Medical Center, Rochester, NY, USA

Department of Neurosurgery, University of Rochester Medical Center, Rochester, NY, USA

Brandon A. Miller, MD, PhD Department of Neurosurgery, Emory University, Atlanta, GA, USA

Gautam U. Mehta, MD Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA

Edward C. Nemergut, MD University of Virginia Health System, Department of Anesthesiology, Charlottesville, VA, USA

Nelson M. Oyesiku, MD, PhD Department of Neurosurgery, Emory University, Atlanta, GA, USA

Sashank Prasad, MD Division of Neuro-Ophthalmology, Department of Neurology, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA

Amar P. Patel, MD Department of Radiology, Neuroradiology Division, Stanford University School of Medicine, Stanford, CA, USA

Margaret Pain, MD Department of Neurosurgery, Mount Sinai School of Medicine, New York, NY, USA

Vivek P. Patel, MD, PhD Department of Radiology, Stanford University School of Medicine, Stanford, CA, USA

Spencer C. Payne, MD Department of Otolaryngology, Head & Neck Surgery, Division of Allergy & Clinical Immunology, University of Virginia School of Medicine, Charlottesville, VA, USA

Kalmon D. Post, MD Department Neurosurgery, Mount Sinai School of Medicine, Mount Sinai Health System, New York, NY, USA

Daniel M. Prevedello, MD The Ohio State University Wexner Medical Center, Department of Neurological Surgery, Columbus, OH, USA

Trevor J. Royce, MD, MS Harvard Medical School, Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA

Martin J. Rutkowski, MD Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA, USA

Stephen Sandwell, MD Neurosurgery Resident PGY-6, University of Rochester Medical Center, Rochester, NY, USA

Roberto Salvatori, MD Division of Endocrinology, Department of Medicine, and Pituitary Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Theodore H. Schwartz Department of Neurosurgery, Weill Cornell Medical College, New York Presbyterian Hospital, New York, NY, USA

Robert A. Scranton, MD Kenneth R. Peak Brain and Pituitary Tumor Treatment Center and Department of Neurosurgery, Houston Methodist Neurological Institute, Houston, TX, USA

Harminder Singh, MD Department of Neurosurgery, Stanford University Medical Center, Stanford, CA, USA

Jason P. Sheehan, MD, PhD Department of Neurological Surgery, University of Virginia, Charlottesville, VA, USA

Department of Radiation Oncology, University of Virginia, Charlottesville, VA, USA

Ismat Shafiq, MD Department of Medicine, University of Rochester Medical Center, Rochester, NY, USA

Department of Neurosurgery, University of Rochester Medical Center, Rochester, NY, USA

Helen A. Shih, MD, MS, MPH Harvard Medical School, Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA

Howard Silberstein, MD, FACS Department of Neurosurgery, University of Rochester Medical Center, Rochester, NY, USA

Luke Smith, MD Department of Neurological Surgery, The Ohio State University Wexner Medical Center, Columbus, OH, USA

Carl H. Snyderman, MD, MBA University of Pittsburgh School of Medicine, Otolaryngology and Neurological Surgery, Pittsburgh, PA, USA

Domenico Solari, MD, PhD Division of Neurosurgery, Department of Neurosciences, Reproductive and Odontostomatological Sciences, Università degli Studi di Napoli "Federico II", Naples, Italy

Alberto Di Somma, MD Division of Neurosurgery, Department of Neurosciences, Reproductive and Odontostomatological Sciences, Università degli Studi di Napoli "Federico II", Naples, Italy

Eleonora F. Spinazzi, BA Department of Neurological Surgery, Rutgers New Jersey, New Jersey Medical School, Newark, NJ, USA

Peter T. Sylvester, MD Department of Neurological Surgery, Washington University School of Medicine, St. Louis, MO, USA

Alissa A. Thomas, MD Department of Neurology, University of Vermont College of Medicine, Burlington, VT, USA

G. Edward Vates, MD, PhD, FACS Center for Translational Neuromedicine, University of Rochester Medical Center, Rochester, NY, USA

Eric W. Wang, MD University of Pittsburgh School of Medicine, Otolaryngology, Pittsburgh, PA, USA

Marilene Wang, MD Department of Head and Neck Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Jonathan Weyhenmeyer, MD Neurosurgery Resident, Goodman Campbell Brain and Spine, Indiana University School of Medicine, Indianapolis, IN, USA

Max Wintermark, MD, MAS, MBA Department of Radiology, Neuroradiology Division, Stanford University School of Medicine, Stanford, CA, USA

Kryscilla Yang, MD Baystate Health, Springfield, MA, USA

Gabriel Zada, MD, MS Neuro-Oncology and Endoscopic Pituitary/Skull Base Program, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Hekmat Zarzour, MD Department of Neurosurgery, Jefferson University Hospital, Philadelphia, PA, USA

Nathan T. Zwagerman, Department of Neurological Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Evolution of Pituitary Surgery and the Transsphenoidal Approach

1

Luke Smith, Gautam U. Mehta, and Russell R. Lonser

Introduction

Although pituitary surgery via the transsphenoidal approach has been performed for over a century, it has only gained widespread acceptance over the past 50 years. As various advances in illumination and magnification through microscopic and endoscopic approaches have improved the safety and efficacy of this technique, it has become the workhorse approach for surgery on the pituitary gland. Further advances, including better understanding of pituitary adenoma biology and improved reconstruction techniques, have extended the utility of this approach to treatment of pathology beyond the sella turcica and its contents. We review the history of pituitary surgery with an emphasis on advances with the transsphenoidal approach.

Early Approaches to the Pituitary

The first recorded surgical approach to the pituitary was performed by Sir Victor Horsley of London in 1889 for pituitary tumor in a patient with visual deficits [24]. Horsley was able to access the pituitary gland using a subfrontal approach, but did not attempt to extirpate the tumor after identifying the tumor as a malignancy with poor prognosis. Early subsequent attempts at transcranial approaches were met with little success and carried high risk of mortality. Caton and Paul, on the advice of Horsley, performed a temporal decompression for a patient with acromegaly.

L. Smith, MD • R.R. Lonser, MD (✉)
Department of Neurological Surgery, The Ohio State University Wexner Medical Center, Columbus, OH, USA
e-mail: russell.lonser@osumc.edu

G.U. Mehta, MD
Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_1

The pair performed a craniotomy to relieve intracranial pressure causing severe pain and distress in the patient. However, the patient was considered too debilitated by her disease to be considered for a surgical resection of her pituitary tumor and died 3 months later of causes that were not mentioned by Caton [5]. With improving surgical conditions at the beginning of the twentieth century, Horsley reported ten operations, using a subtemporal approach, on pituitary tumors with a mortality rate of only 20% [24]. In 1905, Fedor Krause operated on a patient with visual loss using an extradural frontal approach to expose a parasellar "fibrosarcoma" [33]. This would serve as a basis for future transcranial efforts to the sella.

In 1906, a more direct route to the sella turcica was described by Hermann Schloffer. By performing a lateral rhinotomy, reflecting the nose and resecting the turbinates, septum, and sinus walls, Schloffer was able to approach the pituitary gland and partially resect adenoma directly through the sphenoid sinus [41]. He did so without entering the cranial vault, establishing the transsphenoidal approach. A similar operation for a patient with acromegaly was performed by Anton von Eiselberg, later in 1907 [43]. Further improvement of this approach was achieved by Theodor Kocher. While Kocher was awarded the Nobel Prize in 1909 for his work on surgery of the thyroid gland, he made critical contributions to the refinement of the transsphenoidal approach to the sella. This included a submucosal-sublabial variation of the transsphenoidal approach, reducing the cosmetic morbidity of the approach [31]. Inferior nasal variations, which presaged currently used techniques, were described by Oskar Hirsch and Albert Halstead [16, 23]. These sublabial, endonasal transsphenoidal approaches were adopted by Harvey Cushing and used in more than 200 patients with a mortality rate of 6% (Fig. 1.1) [40].

After systematically characterizing and treating many patients with pituitary disease, Cushing became an authoritative figure on this subject. Therefore, when he abandoned the transsphenoidal approach in favor of the transfrontal route, the

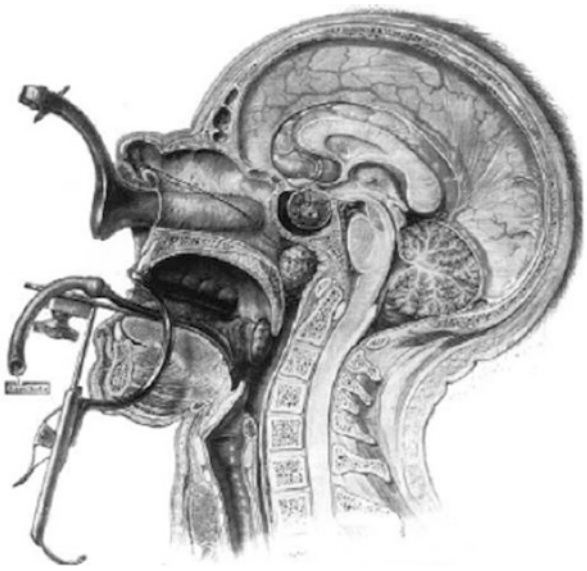

Fig. 1.1 Cushing's sublabial approach [7]

majority of the neurosurgical community followed. He cited improved ability to decompress the optic apparatus as the rationale for the transcranial approach [40]. Work by George J. Heuer to establish a frontotemporal craniotomy further popularized this approach to pituitary pathology [22]. Because the transsphenoidal approach was limited by poor illumination down the long, narrow operative corridor, Norman Dott (a Cushing trainee), who continued to practice the transsphenoidal approach, developed lighted retractors [10]. Dott taught his improved transsphenoidal approach to Gerard Guiot, a French neurosurgeon. Guiot further improved the transsphenoidal approach by using fluoroscopy to confirm instrument trajectory during surgery [21]. Guiot taught the approach to Jules Hardy, who would later repopularize transsphenoidal surgery. Hardy applied the operative microscope to pituitary surgery via the transsphenoidal approach, resolving the challenges of poor illumination and magnification (Fig. 1.2) [17–19].

Hardy described this marriage of microneurosurgery and the transsphenoidal approach [27]:

> My contribution, I think, is when I started to use the surgical microscope, which was an old ENT microscope. And I began to watch carefully what I was doing into the sella and I found that we could identify the normal gland embedded within the mass of tumor tissue. In the past … most agreed that it was impossible to distinguish between normal [gland] and tumor. And whenever we make a sellar cleanout, we remove everything, and all patients would develop panhypopituitarism. With the help of the surgical microscope, we could identify [the pituitary gland]. And that was the first step that I started to claim that we could do selective tumor removal with identification and preservation of the normal gland.

Prior to Hardy's achievement, pituitary surgery was synonymous with total hypophysectomy. The magnification and microneurosurgical techniques introduced

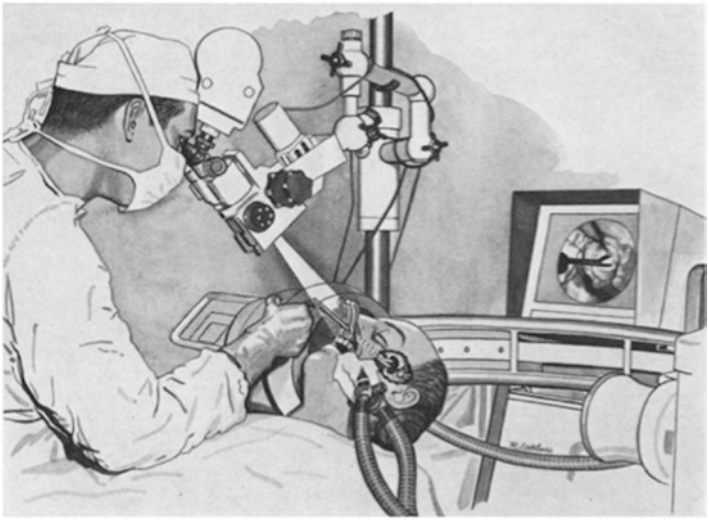

Fig. 1.2 Illustration of Hardy's operative setup of the operative microscope in combination with radiofluoroscopy [19]

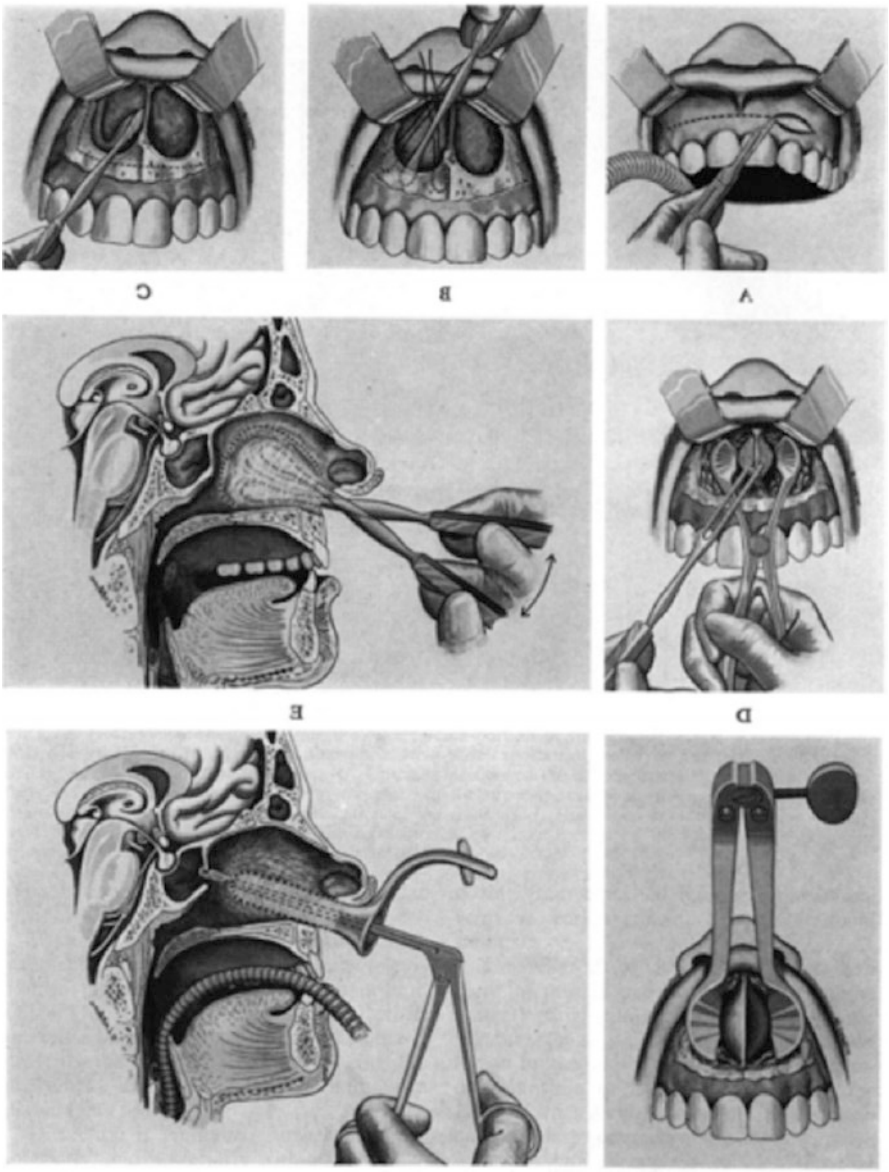

Fig. 1.3 Illustration of the transsphenoidal approach via a sublabial incision as described by Jules Hardy. (**a**) Incision for the sublabial approach. (**b**) Nasal Mucosa elevation. (**c**) Submucosal dissection. (**d**) Excision of the septum. (**e**) Submucosal dissection via sagittal view. (**f**) View after introduction of the speculum. (**g**) Positioning of the speculum via Jules Hardy's approach [19]

by Hardy allowed for surgery within the pituitary gland itself, including selective adenomectomy of endocrine-active microadenomas (Fig. 1.3) [20]. This significant advance coincided with improvements in exogenous hormone replacement that greatly reduced the morbidity of pituitary surgery, which led to more widespread

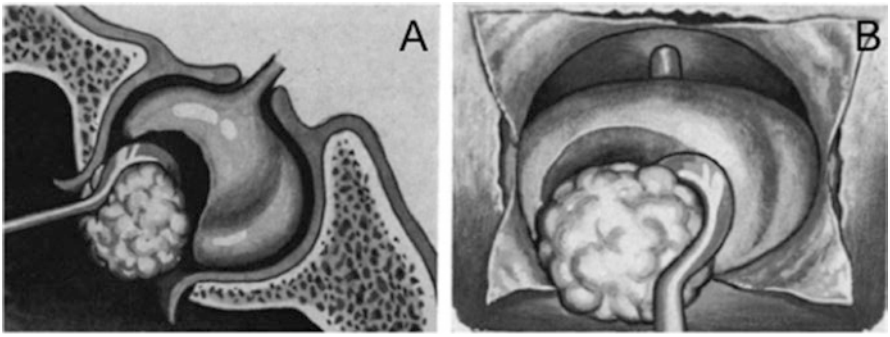

Fig. 1.4 Depiction of selective removal of pituitary microadenoma [19] (**A**) Sagittal view (**B**) Operative (coronal) view.

adoption of the transsphenoidal approach. Later, detailed characterization of outcomes of the approach by Charles Wilson and Edward Laws in the 1970s and 1980s led to greater utilization of the technique [47]. These reports and subsequent studies from other centers established the transsphenoidal approach as a safe (mortality less than 1%) and effective technique for pituitary surgery [2, 6, 34, 46] (Fig. 1.4).

Endoscopy in Transsphenoidal Surgery

Phillip Bozzini developed the first endoscope for use in examining body orifices and wounds [9, 39]. He demonstrated the device, which used candlelight reflected by a mirror, to the Academy of Medicine of Vienna, in 1806. This device provided poor visualization of structures being observed and was large and often painful for patients [37]. Maximillian Nitze, a German urologist, refined this endoscope by adding internalized lighting, using a platinum wire that shone brightly when electricity was conducted through it [37]. He also used a series of lenses to increase the magnifying power of the endoscope. In 1910, Victor Lespinasse, also a urologist, performed the first neuroendoscopy, which he used to treat two children with hydrocephalus [13]. Using intracranial intraventricular endoscopy with coagulation of the choroid plexus, he was successful in one case. However, the other child died postoperatively of unknown causes. In 1922, Walter Dandy described a similar case of endoscopic choroid plexectomy after previously carrying out an open procedure in four other patients [8]. In this case, the procedure was unsuccessful and the choroid plexectomy could not be completed.

Gerard Guiot was the first to apply the endoscope to the transsphenoidal approach [14]. Despite these attempts to use the endoscope in transsphenoidal surgery, Guiot found available iterations of the endoscope difficult to use due to poor visualization and he abandoned the technique. Application of fiber-optic technology to medical endoscopy by Basil Hirschowitz, a gastroenterologist then at the University of Michigan, in 1957, made such applications more practical and more comparable to microscopic alternatives [38, 39]. These improvements led to utilization of pituitary endoscopy as an adjunct to the operative microscope by Michael Apuzzo, in 1977 [1, 3].

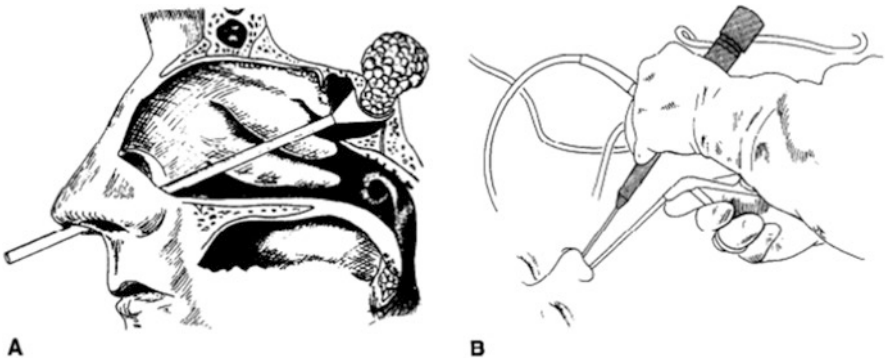

Fig. 1.5 (**a**) Illustration of the endonasal approach to the pituitary. (**b**) Method of holding the endoscope with the surgeon's nondominant hand while surgical instruments are held in the surgeon's dominant hand [26]

He used the endoscope to directly visualize suprasellar extension by tumor that had previously been challenging to observe with the operative microscope and angled mirrors alone [35]. Nasal endoscopy continued to improve during the 1980s, as it was applied to sinonasal surgery, [11] which allowed for the development and improvement of specialized instruments that could eventually be applied to pituitary surgery [42, 45].

These advances in endoscopic sinonasal surgery led to eventual attempts at pure endoscopic pituitary surgery by Roger Jankowski and colleagues in France, in 1990 [25]. They reported a series of three patients in whom they used an endoscope to perform the transsphenoidal pituitary surgery. The utility of this technique was then established by Hae-Dong Jho and Ricardo Carrau (Fig. 1.5) [4]. In 1997, Jho and Carrau reported the safety and feasibility of the pure endoscopic transsphenoidal approach in a series of 50 patients with pituitary tumors [26]. Jho and Carrau's initial series included 44 pituitary adenomas, one craniopharyngioma, one Rathke's cleft cyst, a germinoma, one metastatic adenocarcinoma, and one corrective surgery for post-operative cerebrospinal fluid (CSF) fistula repair. Six of the eight patients with Cushing's disease had a complete resolution of their symptoms. Four patients developed CSF leaks and had prolonged hospitalizations.

Extended Transsphenoidal Approaches

Due to their frequency, pituitary adenomas have been the primary pathology treated via the transsphenoidal approach. Although most are centrally located and are accessible by opening the sella turcica, some lesions may have suprasellar extension that is difficult to resect through this limited exposure. Additionally, nonpituitary parasellar pathology may not be well exposed through the sella alone. These challenges, coupled with the low morbidity of the transsphenoidal approach compared with transcranial approaches, have led to the development of extended

transsphenoidal approaches for suprasellar and parasellar pathology. In 1987, Martin Weiss described an expanded transsphenoidal approach for suprasellar lesions [44]. He described removal of the anterior sellar floor to include the tuberculum sellae and posterior aspect of the planum sphenoidale, allowing direct exposure of suprasellar extension of pituitary adenomas. Edward Oldfield later demonstrated that a similarly extended transsphenoidal approach could be used to resect purely suprasellar tumors, even in the setting of no sellar enlargement [32, 36]. This approach afforded direct access to such lesions and obviated unnecessary manipulation of the normal pituitary gland or a transcranial approach.

Bernardo Fraioli and colleagues, in Italy, improved the lateral visualization of parasellar lesions by incorporating a posterior maxillotomy to further expose the cavernous sinus and the intercavernous carotid artery [12]. As the endoscope can provide a panoramic view and angled endoscopes can be utilized, pure endoscopic transsphenoidal surgery offers enhanced ability to visualize structures in the suprasellar and parasellar space. Capitalizing on these advances, the endonasal operative corridor using the endoscope has continued to expand. Through the work of Amin Kassam and Ricardo Carrau, endoscopic endonasal surgery has been applied to lesions of the anterior cranial fossa, the middle cranial fossa, the clivus, and the foramen magnum [28–30]. With removal of the anterior skull base in such procedures and the difficulty in performing a primary dural repair, one limitation to such expanded techniques had been the significant risk of CSF leak. Recent advances in anterior skull base reconstruction, in particular the development of vascularized, nasoseptal flaps, have greatly reduced the incidence of CSF leak and have enabled more aggressive use of the endonasal approach to address varied pathology [15].

Conclusions

Pituitary surgery, including use of the transsphenoidal approach, has undergone many significant advances over the last century. Although transsphenoidal surgery initially fell out of favor in the early twentieth century, its now widespread use and several timely technological advances have provided a practical and safe operative corridor to the sella turcica, its contents, and beyond.

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The History of Trans-sphenoidal Surgery for Pituitary Tumours

2

James A.J. King and Andrew H. Kaye

Understanding and Diagnosis of Pituitary Tumours

The development of pituitary surgery has evolved based on a progressive understanding of the pathophysiology of these tumours over the past 100 years. This has been underpinned by improvements in radiological imaging of the pituitary region and the development of immunohistochemistry techniques and more recently molecular genetics. Coupled with improvements in technology, surgical instrumentation and lighting, the operations have evolved and progressively become more refined since first undertaken in the modern era by Hermann Schloffer at the University of Innsbruck. There have been innumerable contributors in this process, of which the major participants will be highlighted in this review.

The French physician, Pierre Marie (1853–1940), described two cases of acromegaly from the Pitie-Salpetriere Hospital in Paris in 1886 [45], which he postulated was associated with pituitary hypertrophy [60]. The German physician, Oskar Minkowski, made the observation that pituitary tumours were almost invariably present in acromegaly [46, 65], but the definitive relationship between acromegaly and pituitary tumour was not confidently identified until 1909 [12, 13]. Such advances promoted interest in surgical access to the pituitary as a means of providing treatment, of relieving mass effect and thereby of improving vision and later surgical treatment of endocrine-active tumours.

J.A.J. King • A.H. Kaye (✉)
Department of Neurosurgery, The Royal Melbourne Hospital, Department of Surgery, The University of Melbourne, Melbourne, Australia
e-mail: a.kaye@unimelb.edu.au

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_2

Surgical Approaches

Transcranial Surgery

Transcranial approaches to the pituitary predated the trans-sphenoidal operation and will be briefly discussed. Decompressive procedures were described initially followed by attempts at resection. Sir Victor Horsley (1857–1916), considered to be the first hospital-appointed "neurosurgeon" worldwide in 1886 to the National Hospital in Queen Square [49], attempted surgical resection of a pituitary adenoma via a transfrontal intracranial route in 1889, but the procedure was unsuccessful and unpublished. "My first attention to this subject was drawn by being requested in 1889 to operate on a tumour pressing on the front of the optic chiasma, and for this purpose I raised the frontal lobe, but found that the tumour was really a cystic adeno-sarcoma of the pituitary gland, and was inoperable…". There are no records to support this surgery being performed at the National Hospital, where he was appointed, but it is suggested that it may have been performed outside the hospital [62]. The patient died a few years later with softening of the frontal lobe identified at autopsy. Horsley then published descriptions of ten procedures of both subfrontal and lateral middle fossa approaches to pituitary tumours, often performed in two stages, between 1904 and 1906, with a mortality rate of 20% [30]. This was significantly better than his peers reporting rates of 50–80% at that time [41]. Four operative records were identified from the National Hospital at Queen Square, the first describing actual tumour removal in 1903 (Michael Powell, 2015, Personal communication) [48] (Fig. 2.1).

The first published operation for pituitary pathology was that performed by Caton and Paul of the Royal Liverpool Infirmary, incorporating a lateral extradural subtemporal decompression on February 2, 1893, on a 35-year-old female patient with acromegaly, headache and severe visual loss. The tumour was not resected, and the patient died 3 months after the surgery [7].

The German surgeon-anatomist, Fedor Krause (1857–1937), chief surgeon at the Augusta Hospital at the University of Berlin in 1905 described a frontal transcranial approach to the sella [36]. Krause's approach is stated to have been derived from a procedure he performed in 1900 to remove a bullet from the region of the anterior clinoid process in a man who have been shot 4 years earlier. After elevating an osteoplastic craniotomy flap lateral to the frontal sinus, an extradural approach was performed, until the dura was opened over the bullet. He was then able to visualise the optic nerve and the carotid artery and identified this as a potential approach to the pituitary. Krause wrote "Though the peduncle (infundibulum) of the pituitary arises from the brain behind the chiasm, the hypophysis itself lies in front, beneath its anterior edge" [37]. In 1909, Krause removed a pituitary tumour by this route. Krause subsequently made significant contributions to neurosurgery for epilepsy, trigeminal neuralgia and tumours of the cerebellopontine angle and pineal region [54] (Fig. 2.2).

The cranial approach to the pituitary underwent further modifications, primarily medial or lateral frontal intradural, as continued to be used today. Sir Walter Dandy

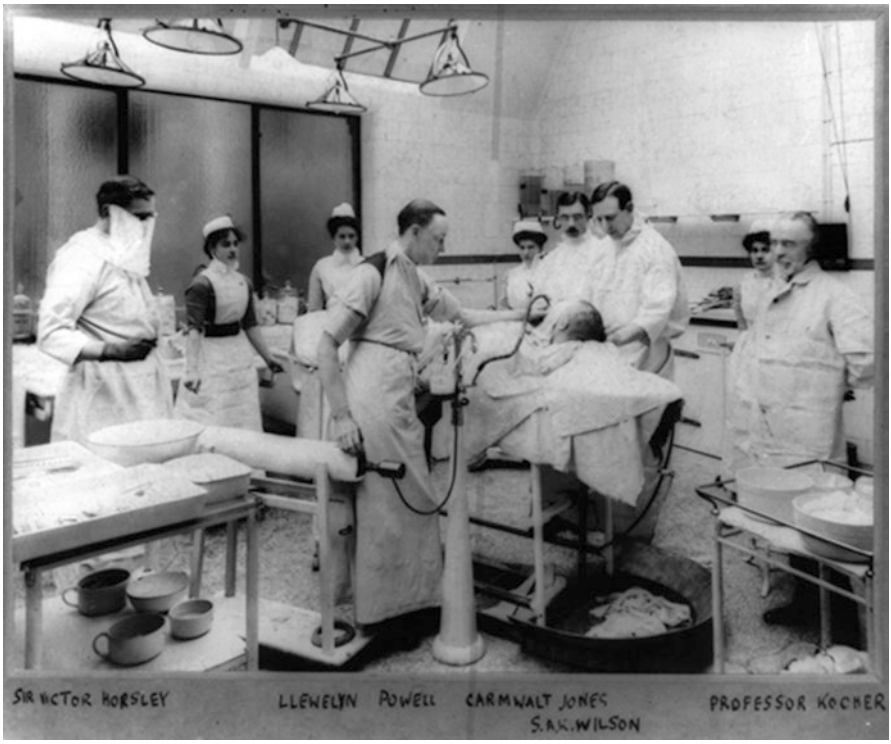

Fig. 2.1 Picture of Horsley and Kocher. Sir Victor Horsley's nineteenth century operations at the National Hospital for Neurology and Neurosurgery, Queen Square [62]. Permission required

Fig. 2.2 Photo of Fedor Krause (Reproduced from Kolle [69]. In [54]. Permission required)

(1886–1946) with Dr. George Heuer (1882–1950) described a lateral anterior fossa approach [15, 29]. Charles Frazier (1870–1936) at the University of Pennsylvania published the details of a fronto-orbital procedure which involved removal of the supraorbital ridge [19]. Harvey Cushing, perhaps the most influential neurosurgeon of the time, favoured a direct transfrontal craniotomy with a right subfrontal midline approach. He utilised this as his favoured approach to the pituitary gland from 1929 onwards. As a consequence of his stature in the field, transcranial approaches dominated until the trans-sphenoidal approach was repopularised by the efforts of Gerard Guiot and Jules Hardy as described later.

Herbert Olivecrona (1891–1980), neurosurgeon working with Rolf Luft (1914–2007), endocrinologist, at the Karolinska Institute in Stockholm in Sweden, published extensively on surgery on the pituitary gland for the treatment of Cushing's syndrome, metastatic breast and prostate cancer, diabetes mellitus and malignant hypertension [42, 43]. The approach is described in detail [42] involving a small lateral frontal flap with intradural exposure of the pituitary, division of the stalk and extirpation of the contents of the sella. Such surgery was made possible with the introduction of cortisone and other hormone replacement therapies.

Another major proponent of the transcranial approach in the mid-twentieth century was Bronson Ray (1904–1993), who served as Cushing's last resident at the Brigham from 1931 to 1932. As chief of the Department of Neurological Surgery at New York Hospital/Cornell University Medical Centre, he performed over 1500 transfrontal hypophysectomies for breast cancer and other disorders [52].

Trans-sphenoidal Surgery

The Egyptians had shown that the intracranial contents could be removed by a trans-sphenoidal route as far back as 1500–100 BC [23]. Perforations in the skull base through the ethmoid and sphenoid sinuses allowed access for a long hook to macerate the brain before removal as a part of the mummification process.

The morbidity and complication rate of transcranial surgery encountered in the late nineteenth century stimulated a search for extracranial routes to the pituitary through the paranasal sinuses. The Venetian anatomist and surgeon, Davide Giordano (1864–1954), described surgical experimentation on cadavers utilising a transnasal route to the pituitary in 1897 [2, 21]. He proposed a transglabellar approach to the pituitary involving resection of the nose and frontal sinus, followed by removal of the ethmoid bone, allowing wide access to the sphenoid sinus and sella.

It was not until Hermann Schloffer (1868–1937), as the director of surgery at the University of Innsbruck, performed removal of a pituitary adenoma in March 1907 was this approach, superior nasal trans-sphenoidal involving a lateral rhinotomy and mobilisation of the nose, used on a living patient [59]. This man was 30 years of age with a history extending over 6 years of headache and visual loss. The diagnosis was based on a radiographic image of an enlarged sella [59]. The surgery was completed after 75 min without complication. The patient successfully recovered from the operation despite 14 days of CSF rhinorrhea, only to succumb some

Fig. 2.3 Portrait of Schloffer (From Lindholm [70], public domain)

2 months after the surgery from hydrocephalus secondary to intraventricular tumour extension confirmed at autopsy [58] (Fig. 2.3).

Schloffer had undertaken extensive study of the anatomy of the paranasal sinuses and pituitary gland in his 51-page dissertation entitled *Zur Frage der Operationen an der Hypophyse* (On the Question of Surgery on the Pituitary), published in *Beiträge zur klinischen Chirurgie* in 1906 [57]. In this, Schloffer wrote "Until now, no such operation has yet been carried out on a living patient, at least none has been reported, obviously, because firstly the decision to perform such a difficult intervention bears the mark of a foolhardy novice, and is difficult even for the expert; secondly because the function of the hypophysis remains obscure and hence the consequences of extirpation of the pituitary cannot be foreseen" [57]. Schloffer performed his first such surgery 1 year later.

This procedure was refined further by Anton von Eiselsberg and Julius von Hochenegg (1859–1940) in Vienna, in 1908 who added resection of the frontal sinuses [63]. Von Eiselsberg reported five cases of meningitis (of which four were fatal) in 16 operations performed using Schloffer's procedure [10]. The high risk of meningitis and the significant postoperative disfigurement necessitated further refinements of the technique.

The legendary Swiss surgeon and Nobel Laureate, Theodor Kocher (1841–1917) working in Berne, described the submucosal dissection of the nasal septum via a complex external incision involving the bridge of the nose in 1909 [35]. His approach provided the advance of confirmation of the midline and was less disfiguring. Kocher's first patient was an acromegalic, and significant symptomatic improvement was documented post-surgery [39].

Ottakar Chiari, a rhinologist working in Freiburg in 1912, performed a superior trans-ethmoidal approach via the medial aspect of the orbit, which offered a shorter surgical corridor but was associated with increased risk to the anterior ethmoidal and the internal carotid arteries [8].

Oscar Hirsch

Oscar Hirsch, a Viennese rhinologist, proposed a direct trans-ethmoidal route without reflection of the nose. He performed this operation in multiple stages over up to 5 weeks, under local anaesthetic with successful visual outcomes. In June 1910, he is credited as the first to perform a submucosal trans-septal approach to the pituitary gland involving a small incision at the columella, the mucosa reflected by a nasal speculum. Subsequently, his colleague and collaborator, the neurosurgeon, Hannibal Hamlin, described Hirsch later in his career, operating with the patient "seated with the head fixed, while awake and under the influence of no other medication. The nasopharyngeal surface was cocainized and the mucosa infiltrated by a local anaesthetic. Hirsch would sit opposite with instruments at hand. Illumination was provided by a reflective-mirrored light, and suction was supplied by a foot-pedal rig operated by a faithful dwarf (an ex-patient named Shostel)" [25].

Hirsch spent his early career in Vienna and performed the procedure for Cushing there in 1911, before moving to Boston in 1938, the year of the Anschluss [25]. Hirsch dedicated his life to trans-sphenoidal pituitary surgery. Working with Hamlin, he performed over 500 cases of pituitary surgery until retiring at 85 years of age. When the trans-sphenoidal approach had been largely abandoned in the USA and Europe, Hirsch continued to perform this procedure in a single sitting, described by Zervas as an "obscure voice in the wilderness [68]".

A colourful description of Hirsch performing a trans-sphenoidal operation in October 1957 was published by Rovit [55] in 2002. It is illuminating and highlights the difficulties encountered by pioneering pituitary surgeons.

> One incident involving Dr. Hirsch stands out in my memory. A 61-year-old woman with hypopituitarism had been followed for years by the staff of endocrine services at MGH. Skull x-ray films revealed progressive ballooning of the sella turcica. Her roentgen findings were so characteristic of an expanding pituitary tumor that they were included in the textbook *Roentgen Interpretation* by Holmes and Robbins. A pneumoencephalogram had demonstrated an intrasellar mass with suprasellar extension, and she had received two courses of radiation therapy. Despite this therapy, and while being maintained on thyroid medication and cortisone, the patient experienced bitemporal hemianopsia with decreased vision in both eyes, especially the left, and a left sixth nerve paralysis. Because of progressive visual impairment, Dr. Hirsch, assisted by Hannibal Hamlin, performed a trans-sphenoidal operation in October 1957.
>
> In this particular case, Dr. Hirsch entered the sella floor without incident, but after a few manipulations, a sudden torrent of bright red blood gushed from the nose under arterial pressure, splashing everything in its vicinity. After the usual instantaneous profanities, Dr. Hirsch calmly said, "This is not the time to curse. This is the time to pray". With that admonition and the loss of several hundred additional milliliters of blood, he skillfully packed the nose and the bleeding was controlled. No further bleeding was encountered when the packing was removed several days later. Subsequent angiography revealed a large internal carotid artery aneurysm that filled the sella. The patient initially did well but eventually died after an intracranial procedure with carotid ligation under hypothermia (Fig. 2.4).

Albert Halstead (1868–1926) of Chicago in 1910 subsequently described the sublabial gingival incision, a modification of the inferior rhinotomy approach of Allen Kanavel, improving access with a reduction in the postoperative defect [24, 34]. This technique was later to be adopted by Cushing.

Fig. 2.4 Drawing of Hirsch's endonasal, submucosal and trans-septal approach to the sella (Reproduced from a slide in Dr. Laws' collection. From Lanzino and Laws [39]. Permission required)

Harvey Cushing

Cushing's early experience of transcranial surgery for pituitary tumours at Johns Hopkins in Baltimore in 1905 was discouraging, and an alternative was sought. Cushing's first trans-sphenoidal patient was a 38-year-old farmer with acromegaly, undergoing surgery involving a tracheostomy, followed by a forehead flap incision to access the paranasal sinuses and sella, on March 25, 1909, under ether-based anaesthesia [9]. Cushing performed his first sublabial trans-septal excision of a pituitary tumour in Boston, it is said on the same day as Hirsch's operation, June 4, 1910, and the two corresponded regarding these procedures [39]. Cushing added the use of a sea sponge placed in the nasopharynx to prevent blood entering the oesophagus and topical adrenaline to assist with haemostasis. By World War I, Cushing had performed over 50 trans-sphenoidal cases, over 20% of his total operations.

Cushing primarily utilised a sublabial submucosal trans-septal approach under intratracheal general anaesthesia, adopting innovations from Allen Kanavel (1874–1938) and Albert Halstead (1868–1926) from Chicago and Theodor Kocher from Berne [13, 14]. In total, Cushing performed 74 pituitary operations at the Johns Hopkins Hospital, followed by 338 hypophysectomies in Boston.

During this period, a significant advance in the diagnosis and surgery for pituitary tumours was the development of pneumoencephalography in 1919 [16]. This for the first time allowed the surgeon to gain preoperative awareness of the presence of suprasellar tumour extension.

Cushing was able to demonstrate a mortality rate of 5.6% in his 231 pituitary trans-sphenoidal cases from 1910 to 1925 [28]. Despite this, Cushing abandoned the trans-sphenoidal approach in 1929 in favour of the transfrontal procedure, particularly when the sella was not enlarged, citing better visual outcomes with craniotomy, better ability to deal with unexpected pathology and greater ease at reoperation. As a consequence of his stature in the field, the majority of neurosurgeons followed his lead (Fig. 2.5).

Fig. 2.5 Drawing of Cushing performing trans-sphenoidal surgery (From Cushing [14]. Permission required)

Norman Dott

Norman Dott (1897–1973) was the exception. Norman Dott was born in Edinburgh in 1897, attending medical school in that city and becoming a resident at the Royal Infirmary of Edinburgh where he was awarded the Fellowship of the Royal College of Surgeons of Edinburgh. Upon being awarded the Rockefeller Fellowship, Dott spent 6 months from November 1923 as Cushing's assistant at the Peter Bent Brigham Hospital in Boston. There he came to observe the sublabial trans-sphenoidal procedure and published in 1925 with Percival Bailey a report of Cushing's 196 patients with pituitary tumours [17].

Dott continued to perform trans-sphenoidal surgery at the Royal Infirmary in Edinburgh and by 1956 had performed 120 such operations. He further developed a lighted speculum retractor to facilitate better visualisation of critical structures at the depth of the surgical exposure.

Dr. J.F. Shaw describes the atmosphere of Dott's operating room. "Now watch Dott carrying out a typical pituitary operation. The patient, lying supine, is covered overall by surgical drapes: only the nose and the mouth are exposed. Dott leans over this area with a headlight on and every now and then adjusts the position of the long

malleable light, held by the assistant. Anxiety lies in the narrowly exposed eye of his assistant who is responsible for maintaining the correct position of this light but can only fleetingly see the deep operation site as he peers first one way then another around Dott's neck and hands. Sister too looks anxious, especially when she sees the light starts to flicker and go out, which, test it as you may before the operation, seems unfailingly to occur at least once during the crucial period.

How Dott would have appreciated the convenience of transaxial illumination of the operating microscope, which was denied him by a matter of years. Sister can see even less of the operating field than the assistant and the confident way she slaps the instruments into Dott's outstretched hand comes only from years of experience and the ability to deduce the stage of the operation from sound and hand movements. She too, in company with the small group of hopeful postgraduate students hovering behind the assistant, seeing little but hanging eagerly on any word or gesture, would have appreciated the modern microscope with its television facility; all would have been shown so clearly, on a nearby screen. So approximately 90 min pass to the noise of the sucker, or of instruments against bone, the silence of soft tissue, the occasional, sometimes testy interjection. Then Dott packs the nose and strips off his gloves. His assistants have been privileged by an occasional fleeting glance of the vital areas" [56].

Dott never published his trans-sphenoidal results, some suggesting this was out of deference to his mentor, Cushing (Fig. 2.6).

During the period of preoccupation of the neurosurgical community with transcranial approaches, otolaryngologists introduced microsurgical trans-ethmoidal hypophysectomy. These were predominantly performed for advanced cancer. Lennart Gisselsson is credited as the first, in Sweden in 1957 using Chiari's approach [65], followed by Niels Riskaer in Copenhagen in 1958. Riskaer published his series of 47 patients with breast cancer in 1961 [53]. Geoffrey Bateman, Ronald Macbeth and John James, all based in England, popularised the technique, describing the use of the drill for poorly pneumatised sphenoid sinus and reduction of cerebrospinal fluid leak by packing of the sphenoid sinus with muscle and fascia.

Gerard Guiot

Gerard Guiot (1912–1998) was instrumental in the reintroduction of the trans-sphenoidal procedure to the neurosurgical community. Gerard Guiot was born in Fourmies in 1912, in Northern France, and graduated from the medical school of Paris in 1937. Guiot trained in neurosurgery under Professor R. Garcin in Paris and also influenced by Clovis Vincent. In 1956, Guiot founded the Department of Neurosurgery at l'Hopital Foch. It was in the same year that Guiot visited Norman Dott in Edinburgh as an observer and was impressed by his use of the trans-sphenoidal technique. "During those two weeks I saw Professor Dott operating two pituitary tumors by the transsphenoidal route. And I remember Pr. Dott telling me the day after: 'look at the postoperative campimetry! The patient is already improved'…he showed me his statistics: no mortality for his last 80 cases…. I was convinced" [39].

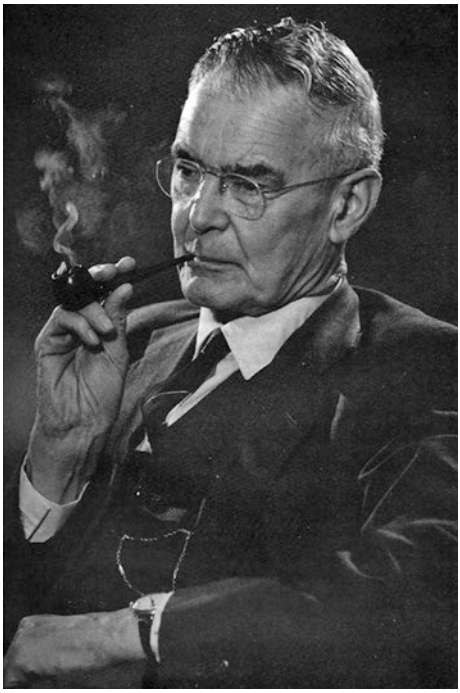

Fig. 2.6 Photo portrait of Norman Dott by Grace Allison, a former patient who had been treated by Dott for a pituitary tumour (Rush and Shaw [56]. Permission required)

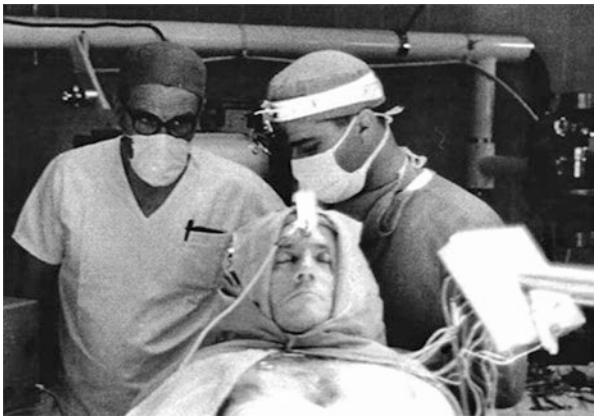

Fig. 2.7 Photograph of Jules Hardy and Gerard Guiot (Reprinted from *Transsphenoidal Surgery*, Laws, ER, Lanzino, G, "History of Transsphenoidal Surgery for Pituitary Tumours" Lanzino, G, Catapano D, and Laws ER, permission required from Elsevier)

Guiot was an innovator and made many significant contributions to neurosurgery including intraventricular endoscopy and stereotaxy, but to pituitary surgery, he added the use of fluoroscopy [38]. Combined with lumbar spinal drain insertion for the administration of air and contrast, Guiot demonstrated greater safety of the trans-sphenoidal approach and the ability to resect those tumours with greater suprasellar extension. His series of pituitary surgery included more than 1500 pituitary adenomas of which more than 200 were performed with fluoroscopic guidance [40]. Significantly he mentored a young French Canadian surgeon, Jules Hardy, who popularised the procedure again in North America (Fig. 2.7).

Jules Hardy

Jules Hardy (1932-) from Quebec trained at the Montreal Neurological Institute and underwent fellowship training with Guiot in Paris in 1961–1962. Hardy introduced trans-sphenoidal surgery to the Notre Dame Hospital at the University of Montreal in 1962 stating "My very first patient had a very large tumor with a supra-sellar expansion; he was blind from one eye and had hemianopsia on the other. I therefore performed a sub-total debulking as Guiot taught me and the patient's vision improved rapidly". Hardy routinely used preoperative angiography and intraoperative air encephalography. Hardy further refined the use of videofluoroscopy "…the major advantage of fluoroscopy was the monitoring of the instrumental manoeuvres on the television screen while removing large pituitary tumors with suprasellar extension. Intermittent views during the progressive descent of the tumor dome, monitored by air injection through the lumbar route or by direct visualization with contrast solution perfusion, afford immediate intraoperative live imaging of the tumor removal..." [26].

Perhaps Hardy's greatest contribution to the field was the introduction of the operative microscope in 1965 to overcome the long encountered difficulties of lighting and vision in trans-sphenoidal surgery. Hardy described the use of the microscope in a case of hypophysectomy for breast cancer on October 13, 1965, and subsequently stated, "at higher magnification I was able to distinguish in some cases the residual normal pituitary gland quite separate from the tumoral tissue. As a result I decided to make all effort to preserve the pituitary to prevent new deficits. This was successful and even more we observed restoration of functions after tumor removal due to relief of pressure upon the normal gland". Hardy reported no deaths or major morbidity in his first 50 microscopic cases [65].

Hardy developed specific instrumentation for the trans-sphenoidal approach and was the first to describe surgery for endocrine-active microadenomas in 1968 which was met with controversy amongst the wider neurosurgical community [61]. Hardy recalls the comment of Bronson Ray "I would like to discourage any effort to revive this old ancient procedure through the nose presented by this young surgeon; the results are not any better than by the intracranial procedure…" [27].

The trans-sphenoidal procedure was then championed by prominent figures in the neurosurgical community, including Edward Laws, Tsutomu Kato, Charles Wilson, Edward Oldfield, Rudolf Fahlbusch and Giorgio Frank. Of these, Edward Laws has performed over 6000 trans-sphenoidal operations, adopting the fully endoscopic approach later in his career, and founder of the International Society of Pituitary Surgeons who first met in Boston in 1983. The development of immunohistochemistry driving better understanding of the pathology and advances in radiology with CT and MRI were critical to surgical progress during this time [66].

Image Guidance and Intraoperative MRI

Fluoroscopy as popularised by Guiot and Hardy has continued to be used to the present day, particularly by microscopic pituitary surgeons, as it affords real-time intraoperative imaging. Frameless stereotaxy/neuronavigation has been widely

adopted and has an important role in patients with complex anatomy and in reoperation but lacks the real-time facility and can be associated with registration error. The use of the endoscope, which affords a panoramic view within the sphenoid and sella, has, to some extent, reduced the reliance on intraoperative imaging. Both ultrasound [3, 51] and microvascular Doppler ultrasonography [18] have been applied to improve the safety of extended endoscopic approaches involving bony removal over the carotid arteries and in tumour removal from the cavernous sinus. Additionally microvascular Doppler has been described as useful in the assessment of the viability of a pedicled nasal septal flap in redo surgery [47].

The evolution of imaging in pituitary surgery has more recently incorporated intraoperative MRI [4, 5]. Proponents of the procedure have documented improved gross total resection rates with iMRI and longer disease-free intervals [4, 5]. The uptake of this technology has been limited. This procedure has been found by some to be cumbersome, costly and perhaps less helpful following refinements in the endoscopic technique. The interpretation of intraoperative images can also be difficult due to image artefact.

Endoscopic Pituitary Surgery

Guiot is credited as the first to describe the use of the endoscope in trans-sphenoidal pituitary surgery in 1963 [22]. The initial descriptions involved use of the endoscope as an adjunct to microscopic approaches [1], until Jankowski from the University of Nancy [31] described the first fully endoscopic sublabial approach to the pituitary in 1992. Hae-Dong Jho and Ricardo Carrau, working at the University of Pittsburgh Medical Centre, are considered pioneers of the pure endoscopic endonasal approach and amongst the founders of modern endoscopic pituitary surgery. Jho describes the development of the procedure in 1993 and in 1997 reported on the first 50 patients treated in this way [32].

Paolo Cappabianca and Enrico De Divitiis from the University of Naples made major contributions to the field of purely endoscopic pituitary surgery, with the development of equipment, evaluation of results and use of extended techniques [6].

Endoscopic pituitary surgery has grown in popularity over the last 20 years with the development of higher-definition camera systems, improved instrumentation and greater acceptance of the technique. Collaboration with otolaryngologists has become a common practice with the development of three- and four-handed surgical techniques. A number of groups have popularised the technique, Kassam and Snyderman, Schwartz and Anand, and others [50].

Extended Trans-sphenoidal Surgery

Both microscopic and endoscopic trans-sphenoidal procedures have been expanded to address parasellar, anterior fossa and clival pathologies [44]. The transplanum approach was described by Weiss in 1987 [64] for the removal of suprasellar lesions.

In 2004, Couldwell reported 105 cases of extended trans-sphenoidal approaches allowing access to the cavernous sinus, suprasellar and clival region [11].

The pure endoscopic technique has been employed to access the skull base from the cribriform plate down to the foramen magnum and odontoid and as far lateral as the foramen ovale [33].

Conclusion

The continuous development and refinement seen in pituitary surgery over the last century will inevitably continue into the future. Three-dimensional endoscopic systems as an advance on widely available 2D systems of today are gaining acceptance, and perhaps the most exciting potential development is the use of robotics [20]. Pituitary surgery would seem well suited to the use of robotics integrated with neuronavigation and other potential adjuncts to resection such as ICG, to facilitate access and vision in deep locations, even potentially to perform procedures remotely [67]. From near abandonment, the future of trans-sphenoidal pituitary surgery looks assured.

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Principles and Pitfalls of Anesthesia for Transsphenoidal Surgery

3

Lauren K. Dunn and Edward C. Nemergut

Background

Pituitary tumors comprise approximately 15% of intracranial neoplasms [1]. They may affect as many as one in six people based on autopsy and radiologic reports, though many of these tumors are incidental findings and do not present a clinical problem [2]. Tumors arise from a single progenitor cell to form a monoclonal adenoma. They are frequently benign and remain confined to the sella turcica and are rarely invasive. Several classification systems exist, including size, hormone secretion, and clinical disease entity. By size, they are classified as microadenomas (<1 cm) or macroadenomas (>1 cm) [1]. Macroadenomas typically present with symptoms of mass effect: increased intracranial pressure, headache, visual disturbances, and cranial nerve palsy. Microadenomas frequently present with symptoms due to excess hormone secretion.

Pituitary tumors are also classified based on hormone secretion as functioning or nonfunctioning. Functioning adenomas are typically composed of a single cell type and produce a single hormone. They are frequently diagnosed due to systemic effects of hormone hypersecretion. Nonfunctioning adenomas do not secrete a hormone and are more likely to be macroadenomas. Among clinically relevant adenomas, prolactinomas are the most common tumor type (66%), followed by null cell (nonfunctioning) adenomas (14.7%), growth hormone (GH)-secreting somatotroph adenomas (13.2%), and adrenocorticotropic hormone-secreting (ACTH) corticotroph adenomas (5.9%) [3]. Less common are thyrotropic adenomas (thyroid-stimulating hormone [TSH] secreting) and gonadotropic adenomas

L.K. Dunn, MD, PhD
University of Virginia, Department of Anesthesiology, Charlottesville, VA, USA

E.C. Nemergut, MD (✉)
University of Virginia Health System, Department of Anesthesiology,
Charlottesville, VA, USA
e-mail: en3x@virginia.edu

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_3

(follicle-stimulating hormone [FSH] and luteinizing hormone [LH]). Functioning adenomas are further described by their clinical presentation: acromegaly (growth hormone excess) and Cushing's disease (ACTH-secreting corticotroph), which have special implications for anesthesia providers.

Medical therapy may minimize the systemic effects of functioning tumors, particularly prolactinomas which are highly sensitive to dopamine agonists (bromocriptine, cabergoline, and pergolide) [4]. However, surgery is the mainstay therapy for patients with prolactinomas unresponsive to medical therapy, as well as patients with acromegaly, Cushing's disease, and nonfunctioning adenomas. The transsphenoidal approach is strongly preferred to transcranial for resection of many pituitary tumors due to the low risk of postoperative complications, particularly with endoscopic procedures [5]. Anesthetic considerations for patients undergoing transsphenoidal surgery for pituitary tumors are presented here.

Preoperative Assessment

All patients presenting for pituitary surgery require a thorough preoperative assessment. Magnetic resonance imaging (MRI) assists in determining lesion size, location, involvement of vascular structures within the cavernous sinus, and additional findings, such as midline shift or obstruction of the third ventricle, which indicate elevated intracranial pressure [5]. Endocrine evaluation includes measurement of pituitary hormones (prolactin, TSH, ACTH, GH, LH, and FSH), as well as downstream hormones (free thyroxine, cortisol, insulin-like growth factor-1 (IGF-1), testosterone, and estradiol) [6]. The releasing and inhibiting factors for each pituitary hormone are summarized in Table 3.1. An ACTH stimulation test can be performed in patients with low serum cortisol levels to determine if preoperative steroids are necessary. Additional considerations for specific clinical conditions will be discussed below.

Prolactinomas

Prolactinomas are the most common pituitary adenoma, but these patients only rarely present for surgery secondary to the success of medical therapy (see below). Women with prolactinomas may present with symptoms of amenorrhea, infertility, galactorrhea, reduced libido, or, in cases of macroadenomas, headache and visual field deficits. Men present with nonspecific symptoms, including erectile dysfunction, impotence, and decreased libido [4]. Dopamine agonists, such as bromocriptine and cabergoline, are a first-line therapy for treating symptoms of hyperprolactinemia. Greater than 90% of microadenomas respond to medical therapy and do not progress to macroadenomas; however, surgery is indicated for patients who fail to respond to medical therapy or to reduce tumor burden in patients with symptoms of mass effect [5]. Women contemplating immediate pregnancy may need surgical resection in order for this to be feasible [5]. Anesthetic management in patients with prolactinomas or other macroadenomas largely focuses on tumor mass effect and minimizing changes in intracranial pressure.

Table 3.1 Major hormones of the anterior pituitary

Hormone	Releasing factor (from the hypothalamus)	Inhibiting factors	Anatomic target	Effects
Adrenocorticotropic hormone (ACTH) (Cushing's disease)	Corticotropin-releasing hormone	Glucocorticoids	Adrenal gland	Secretion of glucocorticoids
Thyroid-stimulating hormone (TSH)	Thyrotropin-releasing hormone	T3 and T4	Thyroid gland	Secretion of thyroid hormones
Growth hormone (GH) (acromegaly)	Growth hormone-releasing hormone	Growth hormone, insulin-like growth factor-1 (IGF-1), somatostatin	Liver, adipose tissue	Growth, anabolic, promotes lipid and carbohydrate metabolism
Prolactin (PRL)	(See text)	Dopamine	Ovaries, mammary glands	Milk production, lipid and carbohydrate metabolism
Luteinizing hormone (LH)	Gonadotropin-releasing hormone	Estrogen, testosterone	Gonads	Sex hormone production
Follicle-stimulating hormone (FSH)	Gonadotropin-releasing hormone	Estrogen, testosterone	Gonads	Sex hormone production

Acromegaly

Acromegaly results from chronic secretion of GH, which stimulates production of insulin-like growth factor (IGF)-1. Together these factors lead to somatic growth and metabolic dysfunction. Features of acromegaly include characteristically enlarged hands and feet. Facial bone and soft tissue hypertrophy of the mandible, nose, mouth, tongue, lips, and laryngeal tissue contributes to airway obstruction and the potential for difficult airway management [4]. Patients presenting with hoarseness should be evaluated for laryngeal stenosis or recurrent laryngeal nerve injury [6].

Additionally, obstructive sleep apnea (OSA) may affect up to 70% of acromegalic patients [7]. Patients should be evaluated preoperatively for symptoms of daytime somnolence, snoring, or apnea, which should raise suspicion for OSA and the risk for perioperative airway compromise. Respiratory depressant medications such as opioids and benzodiazepines should be administered with caution in these patients.

Acromegalic patients are at significantly higher mortality risk (2.4–4.8-fold) [8], largely due to cardiovascular disease. Death is due to cardiovascular causes in 50% of untreated acromegalic patients who die before age 50 [9]. Patients present with hypertension, arrhythmias, conduction abnormalities, coronary disease, cardiomegaly, and congestive heart failure [10, 11]. Echocardiographic changes include left ventricular hypertrophy, increased stroke volume, and cardiac output and diastolic

dysfunction, independent of systemic hypertension [12, 13]. Diastolic dysfunction may progress to acromegalic cardiomyopathy [14], which may improve with treatment but may not be completely reversible if allowed to progress to myocardial fibrosis [15–17].

Patients with acromegaly also develop glucose intolerance, which should be optimized preoperatively. Patients may receive preoperative medical therapy with the goal of normalizing growth hormone secretion, decreasing tumor size, and reducing mortality risk to baseline. Three classes of medical therapies are available: somatostatin analogs (octreotide, lanreotide, pasireotide), dopamine antagonists (bromocriptine, cabergoline), and the growth hormone receptor antagonist, pegvisomant [4]. However, surgery remains the first-line therapy for these patients.

Cushing's Disease

Patients with Cushing's disease present with symptoms of weight gain, fatigue, muscle weakness, depression, loss of libido, hirsutism, acne, and menstrual disorders [18]. Additional findings include high blood pressure, impaired glucose metabolism, hyperlipidemia, and hypercoagulability [4]. Hypercortisolism contributes to the development of systemic hypertension in patients with Cushing's disease. Mechanisms include hepatic production of angiotensinogen, activation of the renin-angiotensin system, increased expression of angiotensinogen II receptor, and inositol triphosphate production, which lead to increased plasma volume and vasoconstriction [6]. Ischemic heart disease and left ventricular hypertrophy with associated changes on EKG (high-voltage QRS complexes and T wave inversions) and echocardiogram findings (intraventricular hypertrophy and diastolic dysfunction) [19, 20] are also common in patients with Cushing's disease [21].

Pulmonary complications include an increased risk for OSA (mild in 33% and severe in 18% of patients) [22]. As with acromegaly, patients with Cushing's disease and symptoms of OSA should be assessed with polysomnography preoperatively. Obesity and gastroesophageal reflux disease may contribute to difficult airway management. Diabetes mellitus and glucose intolerance are also common (20–50% and 30–60% of patients, respectively) [23]. Hyperglycemia (blood glucose >180 mg/dL) should be treated intraoperatively, as this may be associated with an increased risk for infection and poor wound healing [21]. Other findings include proximal muscle myopathy (though this is not associated with an increased sensitivity to neuromuscular blockers), skin fragility which makes intravenous catheter insertion difficult, and risk for osteoporotic fractures which makes proper patient positioning an important concern [6]. Medical therapies such as ketoconazole and metyrapone, which inhibit steroidogenesis, may be used in preparation of patients for surgery; however, surgery remains the first-line treatment [4].

Thyrotropic Adenomas

TSH-secreting adenomas are a rare type of pituitary tumor. Patients present with symptoms of hyperthyroidism (palpitations, tremor, sweating, weight loss) [24]. Patients may be diagnosed with other causes of hyperthyroidism, such as Grave's disease; thus, tumors may be large or locally invasive at the time of diagnosis. Treatment of hyperthyroidism with antithyroid hormone mediation (propylthiouracil) or somatostatin analogs (octreotide) to decrease TSH production may control symptoms and decrease tumor size prior to surgery [25]. The anesthesiologist should be adequately prepared to manage increased ICP due to tumor mass effect and the potential for blood loss if tumors are invading vascular structures within the sella.

Nonfunctioning Adenomas

Nonfunctioning adenomas are the second most common type of pituitary tumor. They frequently present with symptoms of mass effect, including headache, nausea, vomiting, and visual changes due to compression on the optic chiasm. Compression of anterior pituitary may lead to hypopituitarism. Patients with hypothyroidism or adrenal insufficiency should receive hormone replacement therapy prior to surgery [6]. Historically, all patients undergoing pituitary surgery received stress doses of hydrocortisone; however, this is not common practice today, and perioperative steroids are withheld in steroid-naive patients or continued at preoperative doses in those taking chronic steroids [26].

Intraoperative Management

Surgical Factors

Transsphenoidal surgery is the treatment of choice for a majority of pituitary tumors. It has been performed through one of three approaches: endonasal, sublabial, and endoscopic endonasal [5]. The latter is preferred as it is associated with a lower rate of complications, particularly the risk of diabetes insipidus which is estimated to be <5% [27, 28].

A lumbar drain may be placed prior to the start of surgery to facilitate exposure of the manipulation of the cerebral spinal fluid CSF. Air or sterile saline may be injected intrathecally to increase intracranial pressure and displace the tumor down into endoscopic view. In the event of a CSF leak (rate as high as 47% in one study) [29], the lumbar drain may be used to sterilely drain fluid and allow the leak to heal [30].

Hypoventilation has also been recommended as a means to improve surgical exposure through hypercarbia-mediated increases in intracranial pressure (ICP). Aghamohamadi et al. compared the effect of injection of sterile saline into the lumbar drain versus hypoventilation in a study of 52 patients undergoing transsphenoidal

surgery for a pituitary adenoma [31]. All patients received a lumbar drain placed in the L3–L4 interspace prior to surgery. In the first group, sterile saline was injected into the lumbar drain, while in the second group the patients were hypoventilated to increase ICP per surgeon's request. Manipulation of the lumbar drain provided improved surgical conditions (surgeon satisfaction 21 (87.5%) versus 2 (9.1%)) and shortened the duration of CSF leak (1.6 ± 0.24 days versus 5 ± 0.50 days) compared to hypoventilation.

Airway Management

Transsphenoidal surgery is performed under general anesthesia, and the airway may be secured with an endotracheal tube. An oral RAE endotracheal tube is preferred by some surgeons and anesthesiologists. As discussed previously, mask ventilation and intubation may present a particular challenge, especially in patients with acromegaly, due to overgrowth of airway tissues. In a prospective trial of patients with acromegaly, 33 of 128 patients (26%) with a Mallampati class 1 or 2 airway were difficult to intubate, with blind intubation performed in 2% of patients whom conventional airway maneuvers failed to improve view of the airway [32]. Bindra et al. found that modified Mallampati classification (MMC) and extended Mallampati score failed to detect difficult laryngoscopy in 7 of 39 acromegalic patients [33], while Sharma et al. found that MMC and the upper lip bite test failed to predict difficult laryngoscopy in 33% of acromegalic patients [34].

Historically, four grades of airway involvement were described for acromegalic patients: (1) none; (2) nasal or pharyngeal mucosal hypertrophy, normal vocal cords, and glottis; (3) glottic stenosis or vocal cord paresis; and (4) combination of 2 and 3, with routine tracheostomy recommended for grades 3 and 4 [35]. Fiberoptic bronchoscopy is an often used alternative for patients with an anticipated difficult airway; however, this too may prove difficult [36]. Friedel et al. reviewed cases of 32 patients with acromegaly who underwent pituitary surgery. Video laryngoscopy was required for intubation in 7 of 32 patients (21.9%), and 4 of 32 patients (12.5%) required fiberoptic intubation [37]. The first intubation failure rate was 12.5%. Intubating laryngeal mask airways have also been used in patients with acromegaly with a first-attempt success rate for tracheal intubation of 56.2% and an overall success rate of 82%, according to one study [38].

In a retrospective review of 746 patients undergoing transsphenoidal surgery at our institution, 28 patients (3.8%) were difficult to intubate endotracheally [39]. Difficulty intubating occurred three times more frequently in acromegalic patients (9.1%) compared to patients with nonfunctioning pituitary adenomas (2.6%). Among patients with acromegaly, gender and tumor size did not contribute to intubation difficulty. The gum elastic bougie was used as an adjunct and allowed for successful intubation 100% of the time.

Patients with Cushing's disease may have features such as obesity [40] or OSA [41, 42] that have been associated with difficult airway management in some studies. As with acromegaly, the anesthesiologist should have additional airway equipment

available (i.e., multiple sizes of endotracheal tubes, gum elastic bougie, video laryngoscope, intubating laryngeal mask airway (LMAs), and emergency cricothyroidotomy kit). Awake fiberoptic intubation is the safest alternative and is recommended in all patients with concern for a difficult airway and who may be difficult to mask ventilate [21].

Positioning and Preparation for Surgery

After anesthesia is induced and the airway is secured, the head is placed in a Mayfield head positioner which immobilizes it and allows for the use of image-guided frameless stereotaxy for tumor localization [43]. The patient is then placed in a slightly head-up position to facilitate venous drainage. The semi-seated position poses a theoretical risk of venous air embolism (VAE) [44]. There has been one case report of a suspected VAE during a sublabial transsphenoidal tumor resection [45]; however, there are no reports of clinical significant VAE in patients undergoing endoscopic endonasal surgery in this position. Additional monitors for VAE, such as precordial Doppler and end-tidal nitrogen concentration monitoring, are not routinely recommended [6].

Next, the nasal mucosa is infiltrated with a local anesthetic solution containing epinephrine or other vasoconstrictors to improve exposure and reduce surgical bleeding. This may result in significant hemodynamic responses, including hypertension and dysrhythmias [46]. In a retrospective review of 100 patients undergoing transsphenoidal pituitary surgery, systolic blood pressure increased by greater than 50% in more than half of patients following intranasal injection, with an average increase in blood pressure of 60 ± 37 mmHg systolic and 23 ± 22 mmHg diastolic [47]. Cardiac arrhythmias, persistent myocardial ischemia, or myocardial infarction was not observed in this study but has been reported elsewhere [48]. The addition of epinephrine 1:400,000 to 2% lidocaine produces less hemodynamic responses and similar operating conditions as 1:200,000 epinephrine in 2% lidocaine [49]. Many institutions avoid the use of epinephrine altogether and instead use lidocaine-containing phenylephrine [21] or oxymetazoline nasal spray, as is the practice of our institution.

Monitoring

Invasive blood pressure monitoring should be considered in patients with cardiomyopathy, uncontrolled hypertension or symptoms of poor exercise tolerance, or congestive heart failure. However, radial artery catheterization should be performed with caution in patients with acromegaly, as collateral blood flow to the hand may be compromised in up to 50% of patients [50]. The decision to place a central venous or pulmonary artery catheter should be guided by the severity of a patient's cardiovascular disease; however, these and other additional monitors beyond those recommended by the American Society of Anesthesiologists are not routinely used at our institution.

Maintenance of Anesthesia

Anesthetic goals for transsphenoidal surgery are to provide a stable plane of anesthesia, minimize hemodynamic changes, maintain optimal cerebral oxygenation, prevent intraoperative complications, and allow for rapid and smooth emergence to permit neurologic assessment following surgery [21]. Volatile anesthetics, propofol, and remifentanil alone or in combination have been used successfully to accomplish these goals. In one study, 90 patients undergoing transsphenoidal surgery were randomized to receive propofol, sevoflurane, or isoflurane for maintenance of anesthesia [51]. Patients who received propofol and sevoflurane had significantly shorter emergence and extubation times. In addition, patients who received propofol had less hypertension following intubation and improved cognition scores following surgery. Sevoflurane also increases cerebral spinal fluid pressure in normocapnic patients, which may facilitate tumor visualization [52].

Remifentanil prevents coughing prior to extubation and facilitates a smooth emergence [53]. Remifentanil in combination with volatile anesthetics provided improved intraoperative hemodynamic stability and faster emergence times compared to maintenance with volatile alone [54] or in combination with propofol [55]. Remifentanil's short duration of action may lead to postoperative hyperalgesia, and patients should receive a longer-acting opioid to prevent postoperative pain.

Dexmedetomidine has also been investigated as an anesthetic adjunct in patients undergoing transsphenoidal pituitary surgery [56, 57]. It is an alpha-2 receptor agonist with sympatholytic and analgesic properties. In a study of 46 patients undergoing transnasal transsphenoidal pituitary surgery, patients were randomized to receive dexmedetomidine 1 mg/kg bolus over 10 min followed by a maintenance infusion of 0.7 mg/kg/h versus normal saline placebo [57]. The dexmedetomidine group had improved hemodynamic stability, including less hypertension and tachycardia following intubation, surgical incision, and extubation, and lower anesthetic requirements and shorter time to emergence and extubation compared to control. Dexmedetomidine was also associated with improved surgical conditions (based on the surgeon's determination of blood loss and dryness of the surgical field) and reduced blood loss compared to placebo.

Salimi et al. reported similar results in a study of 60 patients undergoing transsphenoidal surgery randomized to receive either dexmedetomidine infusion (0.6 mcg/kg/h) versus normal saline placebo [58]. Heart rate and mean arterial pressure were significantly lower throughout surgery in the dexmedetomidine group compared to placebo. In addition, dexmedetomidine was associated with decreased opioid use, less surgical bleeding, and greater surgeon satisfaction with operating conditions compared to placebo.

Muscle relaxation should be used throughout the procedure as patient movement could lead to CSF leak or vascular or optic nerve injury. Patients should be adequately reversed prior to extubation.

Transsphenoidal pituitary surgery is typically associated with minimal blood loss. However, the risk of vascular injury to the internal carotid artery or the cavernous sinus is approximately 1% [59]. Carotid artery injury may result in brisk blood loss.

The surgeon may request induced hypotension in order to visualize and control bleeding. The anesthesiologist should have access to an extremity to place additional intravenous access if necessary. Other surgical complications include nasal bleeding (1%) or septal perforation (2%) or CSF leak (2–3%) [59, 60]. A Valsalva maneuver may help to check for a CSF leak, and if one is identified, the surgeon may use fat or muscle to pack the leak prior to closing the sella [6]. At the completion of surgery, the nose is packed and stomach and oropharynx suctioned to remove emetogenic blood and irrigation fluid. An oral airway may be used to prevent airway obstruction following extubation.

Postoperative Considerations

Postoperative care of patients undergoing pituitary tumor resection includes management of postoperative pain, nausea, and vomiting and monitoring for surgical complications, including CSF leak, meningitis, cranial nerve injury and visual field deficits, neuroendocrine abnormalities, and hypopituitarism. These complications are discussed below.

Pain

Headache pain is a common complaint following transsphenoidal surgery. In a retrospective review of 877 patients who underwent transsphenoidal pituitary surgery, greater morphine consumption in the postanesthesia care unit was associated with a higher likelihood of developing diabetes insipidus postoperatively [61]. Opioids and non-opioid analgesics such as acetaminophen or ketorolac are frequently used to treat postoperative pain. If remifentanil is used for maintenance of anesthesia, the use of a longer-acting opioid pain medication is recommended to prevent hyperalgesia after surgery. As discussed previously, opioids should be used with caution in patients with OSA at risk for respiratory depression. Other non-opioid analgesics include dexmedetomidine [57] or regional techniques, including placement of bilateral infraorbital nerve blocks [62], which may be useful adjuncts for postoperative pain.

Nausea and Vomiting

Nausea and vomiting are common postoperative complications in neurosurgical patients, with a reported incidence of 39% [63]. In their retrospective review, Flynn et al. found the incidence of postoperative vomiting to be 7.5%, much less than other neurosurgical procedures [61]. Risk factors for postoperative vomiting included CSF leak and fat grafting, the use of a lumbar intrathecal catheter, and craniopharyngioma resection. Antiemetic prophylaxis with ondansetron or droperidol prevented nausea but did not prevent emesis after surgery. Vomiting is detrimental

because it may lead to increased ICP, CSF leak, or hemorrhage [64]. Prophylactic antiemetics, such as ondansetron, are routinely given. Dexamethasone effectively prevents postoperative nausea and vomiting, but should not be used following transsphenoidal pituitary surgery as it will interfere with postoperative monitoring of serum cortisol levels. Serum cortisol levels are routinely monitored postoperatively to determine recovery in patients with Cushing's syndrome or to detect hypopituitarism following extensive surgical resection [65]. Following an 8 mg dose of dexamethasone, serum cortisol levels decrease to less than 5% of baseline, with the nadir at 24 h and return to baseline at 48 h [66]. Thus, the perioperative administration of dexamethasone can make the documentation of a successful adenoma resection in patients with Cushing's disease more difficult.

CSF Leak, Cranial Nerve Injury, and Visual Field Deficits

CSF leaks are frequently identified prior to surgical closure; however, they may present postoperatively with rhinorrhea or continuous fluid leaking down the back of the throat. Fluid may be tested for tau transferrin and, if positive, would support the diagnosis of a CSF leak [26].

A thorough neurologic exam should be performed immediately after surgery to assess for visual field deficits, changes in visual acuity, or palsy of cranial nerves II–VI, caused by hemorrhage or compression during surgical resection. The incidence of new visual field deficit or new cranial nerve palsy after transsphenoidal surgery is 0.5–1% [59]. If a new, focal neurologic deficit is found, computed tomography or magnetic resonance imaging should be obtained. Based on these findings, the patient may require urgent re-exploration in the operating room.

Hypopituitarism and Postoperative Hormone Screening

Up to 27% of patients with preoperative hypopituitarism will have normalization of function after tumor resection [67]. Patients receiving steroids for hypopituitarism preoperatively and who received stress doses during surgery are rapidly weaned to baseline on postoperative day 1. Hypopituitarism may develop postoperatively if the anterior pituitary is injured during surgical resection and has been shown to complicate 10–14% of procedures [59]. Morning cortisol levels are monitored through postoperative day 3 and steroid supplemented if levels are <10 mcg/dL or patients have symptoms of adrenal insufficiency (hypotension, anorexia, nausea, vomiting, headache, and myalgias) [26]. In patients with Cushing's disease, cortisol levels are monitored at routine intervals (e.g., every 6 h) to determine adequacy of surgical resection. Similarly, acromegalic patients should have growth hormone levels monitored postoperatively.

Disorders of Water Balance: Diabetes Insipidus (DI) and Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

Disorders of water balance resulting from altered ADH secretion are common postoperative complications following transsphenoidal surgery. The incidence of DI is reported to be between 1% and 14% and syndrome of inappropriate antidiuretic hormone (SIADH) reported as 1–8%, according to one systematic review [27], but other studies report incidences as high as 25% [6]. ADH is produced in the supraoptic and paraventricular nuclei of the hypothalamus and transported to and released from the posterior pituitary. ADH binds to V2 receptors in the renal collecting tubule and promotes insertion of aquaporin channels into the cell membrane. These channels allow passive resorption of water from the collecting ducts [26]. Disruption of the hypothalamus, pituitary stalk, or posterior lobe of the pituitary gland during pituitary surgery may lead to impaired or absent ADH secretion.

DI typically presents in the first 24–48 h after surgery and is usually transient. Symptoms of polyuria, thirst, and polydipsia are accompanied by production of voluminous (4–18 L/day) and dilute (specific gravity <1.005) urine [26]. The development of severe dehydration, volume contraction, hypernatremia, and hyperosmolarity is rare, as most patients are awake and have intact thirst mechanisms and access to fluid after surgery [6]. Screening for DI includes monitoring of daily weights, fluid intake and output, and serum sodium levels. Desmopressin (DDAVP), a synthetic ADH analog administered orally, intranasally, or intravenously, is available to treat DI, but is usually only necessary when serum sodium levels increase above 145 mEq/L, there is a significant discrepancy between fluid intake and output, or urine output interferes with sleep [26].

In a retrospective review of 881 patients undergoing transsphenoidal pituitary surgery at our institution, the incidence of postoperative DI was 18.3%, with 12.4% requiring treatment with desmopressin [68]. Other risk factors for DI were intraoperative CSF leak (33.3% transient and 4.4% persistent DI), craniopharyngioma and Rathke's cleft cysts, and Cushing's disease (22.2% transient DI). Patients with microadenomas were more likely to develop DI than those with macroadenomas (21.6% versus 14.3%).

SIADH is characterized by euvolemia, hypoosmolarity, and hyponatremia (sodium <135 mEq/L). Free water intake exceeds excretion and urine is inappropriately concentrated. This is in contrast to other causes of hyponatremia, such as cerebral salt wasting, which is associated with a volume-contracted state [6]. The onset is delayed, frequently presenting up to a week after surgery [69, 70]. Symptoms depend on the severity and rapidity of onset and may include headache, agitation, anorexia, nausea, vomiting, lethargy, or seizures in severe cases (sodium <115 mEq/L) [26]. Treatment for SIADH in an awake patient with mild symptoms is fluid restriction. Hypertonic (1.8% or 3%) saline should be considered for patients with severe hyponatremia (sodium <120 mEq/L) or those with symptoms of altered mental status or seizures. Sodium levels should not be corrected at a rate greater than 1 mEq/L/h due to the risk of central pontine myelinolysis [26].

Conclusion

Pituitary tumors are common, and patients presenting for transsphenoidal pituitary surgery present unique challenges for the anesthesiologist. Knowledge of hormone function and systemic effects is essential. Attention to airway management and cardiopulmonary risk factors is particularly important in patients with acromegaly and Cushing's disease. Anesthesia for transsphenoidal surgery requires careful preoperative assessment; intraoperative management designed to provide hemodynamic stability, minimize surgical risk factors, and provide rapid emergence; and postoperative care to identify complications including bleeding, CSF leak, visual field deficits, hypopituitarism, DI, and SIADH.

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Operative Indications and Pitfalls in Patient Selection for Surgery of Pituitary Tumors

4

Chikezie Eseonu, Christina Jackson, and Alfredo Quinones-Hinojosa

Preoperative Evaluation

Pituitary tumors generally present in three distinct ways (1) mass effect of the tumor on surrounding structures, (2) hormonal imbalance, and (3) incidental finding on head imaging [1]. An in-depth preoperative evaluation is needed for patients who are potential surgical candidates. Evaluations in radiology, anatomy, endocrinology, and ophthalmology are needed prior to pursuing surgery.

Radiological Diagnosis

Integral to the preoperative evaluation of a pituitary tumor is the radiological diagnosis of the lesion. Magnetic resonance imaging (MRI) with gadolinium is the most prevalent imaging used for pituitary tumors [2]. The MRI allows for visualization of the pituitary tumor as well as establishes the relationship of the tumor with the surrounding anatomy (i.e., optic chiasm, cerebral arteries). Thin-cut computed tomography (CT) scans help illustrate the bony anatomy of the sellar floor [2].

Mass Effect The pituitary gland resides in the sella of the skull base which is surrounded by many structures that can be affected by tumor mass effect (Fig. 4.1). The optic chiasm lies above the pituitary gland within the suprasellar cistern, separated

C. Eseonu, MD • C. Jackson, MD (✉)
Johns Hopkins Hospital, Neurosurgery, Baltimore, MD, USA

A. Quinones-Hinojosa
Mayo Clinic Neurosurgery, Jacksonville, FL, USA
e-mail: quinones@mayo.edu

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_4

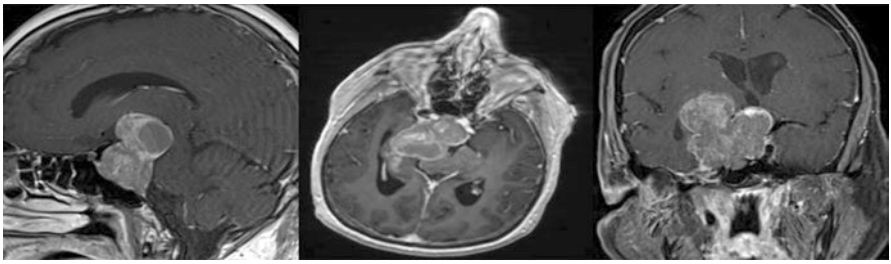

Fig. 4.1 A large sellar/suprasellar heterogeneous enhancing mass that invades into the right cavernous sinus and middle cranial fossa. The lesion also has marked mass effect on the right deep white matter, basal ganglia, thalamus, midbrain, third ventricle, and optic chiasm

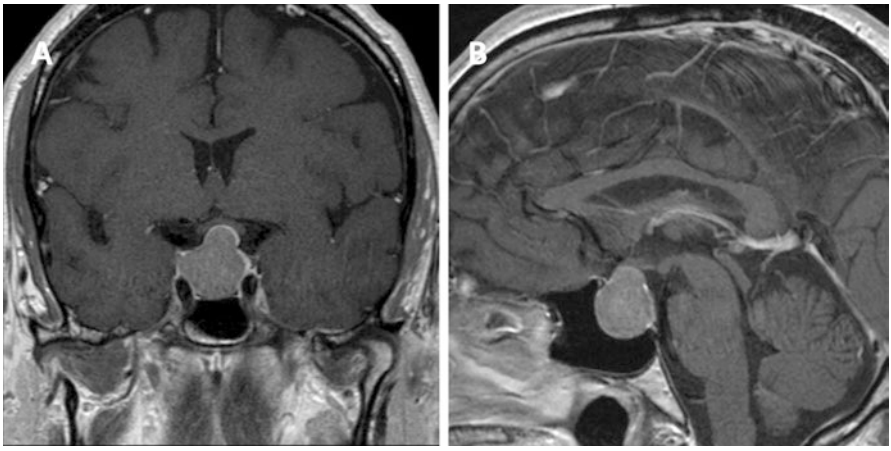

Fig. 4.2 T1-weighted MRI with gadolinium depicting a suprasellar extension of a pituitary tumor with compression of the inferior optic chiasm in the (**a**) coronal and (**b**) sagittal views

by the diaphragma sellae, a leaflet of the dura mater. The pituitary stalk penetrates this leaflet to get to the pituitary gland. The position of the chiasm in relation to the sella can vary patient to patient. Fifteen percent of patients have the chiasm located above the tuberculum sella (prefixed), while 5% of patients have the chiasm located above the dorsum sella (postfixed), and the majority of patients have the optic chiasm directly above the sella. At the optic chiasm, the nasal ganglion retinal axons decussate and join the uncrossed axons from the other eye to create the optic tract [3, 4].

The cavernous sinuses, which contain cranial nerves III, IV, V1, V2, and VI as well as the internal carotid arteries with sympathetic fibers, establish the lateral aspects of the sella [4]. The supraclinoidal ICA is located laterally to the optic chiasm, and the anterior cerebral and anterior communicating arteries are superior and anterior to the chiasm. The posterior communicating and posterior cerebral arteries are posterior and inferior to the chiasm [5].

Large pituitary tumors can often cause suprasellar compression on the optic chiasm that exerts mass effect on the optic chiasm's vascular supply and axons (Fig. 4.2). Visual symptoms can present with progressive loss of vision, decreased

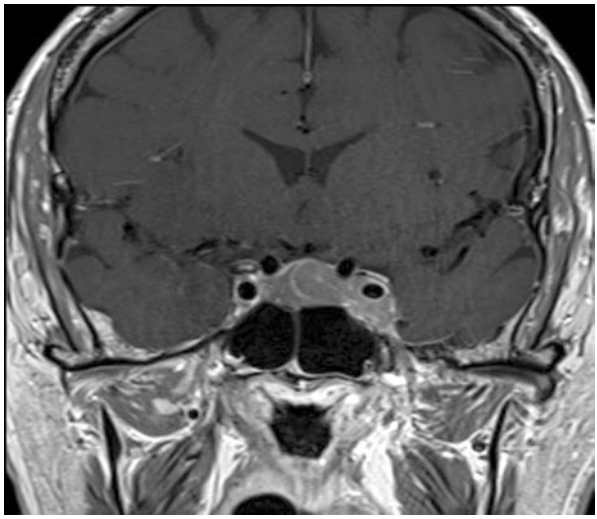

Fig. 4.3 T1-weighted MRI with gadolinium depicting a sellar pituitary tumor with extensive lateral invasion of the left cavernous sinus

brightness, poor color perception, or loss of peripheral visual field. Lateral extension of the pituitary tumor into the cavernous sinus can cause oculomotor problems of diplopia or ptosis [4, 6] (Fig. 4.3). The visual compromise can develop gradually with pituitary adenomas, and surgical decompression is indicated unless the compression can be resolved medically. For acute, severe vision loss that could happen with pituitary apoplexy, surgery is the most reliable method of decompression [7] . In nonsecreting pituitary tumors causing compression, no reliable alternative treatment to surgery has been found to effectively treat the mass effect of the lesion [8].

Pitfall

- When considering surgery for mass effect, the benefit of restoring normal pituitary function must be weighed against the risk of causing worsening hypopituitarism.

Incidental Finding Incidentally found lesions are often treated conservatively; however, the progressive growth of the lesion can be an indication for surgery [9]. Since surgical results correlate with size and extension of the lesion, early surgery on a small, progressing lesion is preferable to a large extensive mass [8]. A pituitary tumor smaller than 1 cm in diameter can be completely resected in 80–90% of cases, whereas tumors greater than 1 cm diameter can be completely resected in 50–60% of cases [10]. Tumors larger than 2 cm in diameter are completely resected in 20% of cases [11]. The location of the tumor also influences outcome. Lesions that are limited to the sella are relatively easier to remove through a transsphenoidal approach. Once a tumor begins to extend into the cavernous sinus, complete resection becomes difficult [4]. The vascularity of the pituitary mass or large venous sinuses can produce profuse intraoperative bleeding that could cause abandoning the surgery [4].

Rhinological Evaluation

The transsphenoidal approach for pituitary tumors has been an evolving technique that requires a good understanding of the normal nasal anatomy and its variations. Transnasal approaches require access to the pituitary via the nostrils. The skin of the nose can influence the nasal support, with the upper portion of the nasal skin being thin and the lower part of the nasal skin being thick and sebaceous which can cause nasal obstruction. The size of the nostrils can also be variable and may affect the decision-making process for the surgical planning route [12].

Patients with complaints of nasal congestion, obstruction, infection, or postnasal drip should be evaluated with a nasal endoscope preoperatively to evaluate middle and posterior aspects of the nose. A sinus CT can be used to evaluate for possible sinus infection. Septal deviation can occur in the anterior, caudal aspect of the cartilaginous septum or in the posterior bony septum [12].

Pitfalls

- Congenitally small, traumatized, or twisted noses may limit the transnasal approach.
- Previous nasal surgery can make nasal mucosal flaps and septal dissections very difficult. Septal perforations can also distort the planes of dissection.
- External features of the nose, such as saddle nose deformity, describe a loss of dorsal septal support, or the twisted nose deformities of the nasal bone and dorsal cartilaginous septum can limit transnasal access.

Endocrinology Evaluation

All patients with a pituitary tumor require preoperative laboratory blood values drawn prior to surgery. This evaluation should include a complete blood count to identify hematologic abnormalities. Coagulation labs should be obtained to ensure proper coagulation profile. A blood urea nitrogen will identify renal function. Metabolic abnormalities are identified using a basic metabolic panel (BMP). High sodium levels may indicate an abnormality with the posterior pituitary with diabetes insipidus (DI), or hyperkalemic alkalosis may indicate a patient with Cushing's disease [1].

Additionally, the endocrine evaluation will require measurements of pituitary hormones as well as certain hormones from the target glands. These include thyroid panel (thyroxine T4, TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), cortisol, adrenocorticotrophic hormone (ACTH), prolactin (PRL), and insulin-like growth factor 1 (IGF-1).

Hormonal Imbalance The proximity of pituitary tumors near the pituitary gland, infundibulum, and hypothalamus makes hormonal abnormalities, either hyper- or hypopituitarism, a common presenting sign with these lesions.

With hyperpituitarism, or hormone oversecretion, surgery is generally indicated for patients with Cushing's disease, thyrotropinomas, acromegaly, or Nelson's syndrome, all of which have hormonal oversecretions that can lead to morbidity and death [9]. Medical therapies (i.e., somatostatin analogues) do exist for this GH- and TSH-secreting pituitary lesions, but surgery has been shown to be the cheaper and more rapidly acting alternative [13]. For ACTH-secreting tumors, medical therapy exists for short-term treatment; however, long-term therapy requires surgery for the pituitary lesion [14].

For hypopituitarism, some literature has shown that low hormone secretions as a result of tumor compression on the pituitary gland can be considered an indication for surgery, since decompression of the pituitary can lead to improved hormonal function [15, 16]. Hypopituitarism from the tumors mass effect can present with hypothyroidism which would need to be normalized prior to surgery. In addition, patients with suppression of the adrenal system and low cortisol levels would need to also be corrected preoperatively. This can also cause patients to have a poor stress response to surgery, which will require a steroid supplementation prior to surgery [1]. Specific hormone-secreting adenomas will be discussed later in the chapter.

Neuro-ophthalmology

An ophthalmology evaluation by a neuro-ophthalmologist is needed for a patient with a pituitary lesion given the close proximity of the pituitary gland to the visual pathway and cranial nerves in the cavernous sinus. Visual compromise from a pituitary tumor can be an indication for surgery. An oculomotor exam is needed to evaluate the range of extraocular movement as some pituitary tumors can cause ophthalmoplegia or ophthalmoparesis. Assessments of visual acuity, color vision, and pupils can assess for problems with the optic pathway, while visual field assessments can aid with localizing the tumor compression.

Visual acuity and color vision loss can be a sign of optic nerve compression in one or two eyes. Color vision abnormalities often present in the form of an inability to distinguish red and green [17]. Pupillary examinations may reveal anisocoria, if there is a disturbance with the sympathetic or parasympathetic nerves. Afferent pupillary defects (APD) are a rare finding with these tumors, although it may occur when there is damage to the efferent parasympathetic component of the third nerve causing abnormal pupillary response to light [18]. The visual field test can assess for visual deficits as a result of compression along the optic pathway. Temporal and monocular defects can be localized to the optic chiasm and optic nerve, respectively, with high sensitivity and specificity [19].

Chiasmal compression by pituitary tumors is often seen and can present as anterior chiasm, midchiasm, or posterior chiasm syndrome. Anterior chiasmal syndrome, also known as junction scotoma, presents with a central scotoma in the ipsilateral eye and a superotemporal field defect in the contralateral eye caused by a lesion that is anterior to the chiasm [20]. Midchiasm compression is most common and causes bitemporal hemianopsia or bilateral superior quadrantanopia (Fig. 4.4).

Fig. 4.4 Visual field of a patient with bitemporal hemianopsia, OS, *left*; OD, *right*

Posterior chiasmal compression is often seen in patients with a prefixed chiasm and shows an asymmetric homonymous hemianopsia from compression of the optic tract [19].

Surgical Indications by Lesion

Following evaluations by the neurosurgeon, endocrinologist, and neuro-ophthalmologist, the decision must be made about whether surgery is the best option for the patient. Although some scenarios may be difficult to determine the best treatment strategy, most pituitary tumors provide clear indications for treatment.

Prolactinomas

Patients tend to present with pituitary adenomas between the fourth and sixth decade of life [39]. Prolactinomas consist of the most common secreting pituitary adenoma [21]. The first line of therapy for prolactinomas is medical treatment, and 90% of patients have been shown to respond to medical therapy with a dopamine agonist (bromocriptine or cabergoline) [22]. Normalization of prolactin levels occurs following medical treatment leaving few patients with prolactinomas as a candidate for surgery [23]. With macroadenomas, PRL should be >200 ng/L in order to be considered a prolactinoma, which would indicate medical management.

Nonresponders to medical therapy, or patients that cannot tolerate the dopamine agonist drugs, are then considered surgical candidates [8].

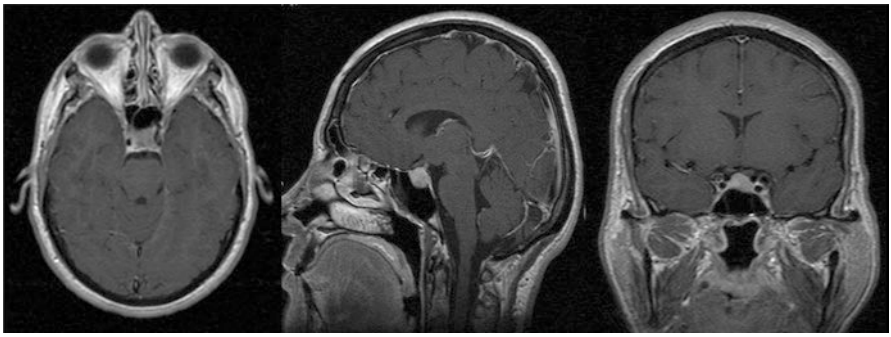

Fig. 4.5 Growth hormone-secreting pituitary mass abutting the optic chiasm in the (*left*) axial, (*middle*) sagittal, and (*right*) coronal planes

Pitfall

- Some prolactinomas can contain hemorrhagic or cystic components that would not respond well to medical therapy and would require surgery to decompress the tumor [4].

Acromegaly

The hypersecretion of growth hormone can lead to increased liver production of somatomedins (i.e., insulin-like growth factor 1 (IGF-1)) (Fig. 4.5). In children, this can cause gigantism, while in adults, this develops acromegaly [1]. Surgery for acromegaly causes endocrine remission in 50% of cases; however, it provides a significant fall in GH and IGF-1 levels. This drop in levels causes improved response to subsequent treatment options [24]. Somatostatin analogs are the primary medical therapy to normalize growth hormone secretion and can reduce tumor size, but should be used as adjuvant therapy to surgery [25, 26].

Pitfalls

- Cardiovascular disease is the most common cause of death in an untreated acromegaly patient [27–29]. Between 10% and 20% of the patients diagnosed with acromegaly have heart failure at diagnosis [28, 30–32]. Oftentimes, this presents as a myocardial hypertrophy [27]. Echocardiography can reveal left ventricular hypertrophy, stroke volume, and cardiac output [32]. Acromegalic cardiomyopathy can consist of diastolic dysfunction and a poorly compliant left ventricle [31]. Careful history and physical exam are needed for acromegaly patients regarding their cardiac status. Symptoms suggestive of cardiac heart failure will warrant a cardiology consultation preoperatively.

- Respiratory disease can also be present in acromegaly. Obstructive sleep apnea (OSA) can be present in as many as 70% of acromegaly patients [33]. In addition, thickening of the laryngeal and pharyngeal tissue can worsen airway obstruction and lead to difficulties with intubation [34]. The tissue thickening along the respiratory tract can also make patients intolerable to nasal packing, which could worsen their OSA [35].

Cushing's Disease

Cushing's disease presents with excessive secretion of adrenocorticotropic hormone (ACTH) by the pituitary adenoma causing hypercortisolism (Fig. 4.6). The increases in circulating cortisol can cause many pathophysiologic effects on a patient including weight gain, purple striae, muscle atrophy, osteoporosis, excess hair growth, kidney stones, and impaired immunological function. Cushing's disease has a high risk of morbidity and mortality and requires a complete resection on the first surgery. Residual tumor in hypercortisolism justifies a repeat surgical resection [4].

Pitfalls

- Systemic hypertension can be a manifestation in 80% of Cushing's disease patients [36]. EKG abnormalities in the form of inverted T waves and large QRS complexes indicative of left ventricular hypertrophy and strain have been reported that can complicate surgery [37].
- OSA is also common in 33% of Cushing's disease patients, as well as centripetal obesity and weight gain, which are common symptoms that can pose complications with intubation [34].
- Glucose intolerance is present in 60% of Cushing's disease patients, and diabetes mellitus is found in a third of the patients [38]. Careful consideration must be taken with ensuring that patients who take oral hypoglycemics do not take these the morning of surgery, since they will be unable to eat prior to surgery.

Thyrotropic Adenoma

Thyrotropic adenomas that produce excess TSH are a rare presenting tumor that accounts for 2.8% of pituitary tumors [39] (Fig. 4.7). This causes a clinical presentation of hyperthyroidism which consists of heart palpitations, tachycardia, weight loss, tremors, and heat intolerance. Propylthiouracil can decrease the amount of thyroid hormone that is produced, while somatostatin analogs can suppress the production of TSH [40]. Although thyrotropinomas are sensitive to these medical therapies, surgery should be attempted first for surgically accessible lesions for complete resection or debulking [4].

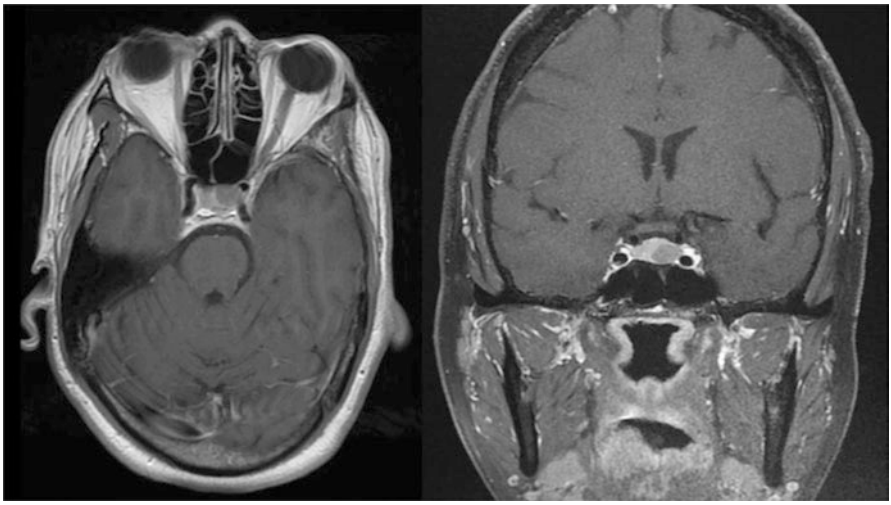

Fig. 4.6 A hypointense mass in the left pituitary gland consistent with ACTH-secreting pituitary microadenoma in the (*left*) axial and (*right*) coronal planes

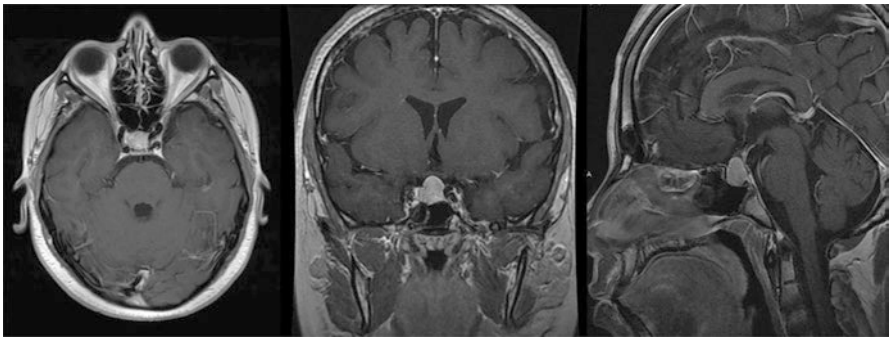

Fig. 4.7 TSH-secreting tumor in the anterior pituitary gland extending into the suprasellar space in the (*left*) axial, (*middle*) coronal, and (*right*) sagittal planes

Pitfall

- The hyperthyroidism must be controlled prior to a patient undergoing surgery since hemodynamic instability can put the patient at risk during the operative procedure. Preoperative management of hyperthyroidism manages the risk of preoperative cardiac arrhythmias for TSH-producing tumors [41].

Nonfunctioning Tumors

In addition to mass effect on surrounding structures, nonfunctioning adenomas as well as other tumors found in the sellar region often cause local mass effect on the pituitary which can cause hyperprolactenemia from stalk effect, where there is a decrease in dopamine-mediate inhibition of prolactin release. In these cases, the serum prolactin level is <200 ng/L. As discussed earlier in the chapter, larger tumors would require surgical resection, while smaller lesions can be followed with serial imaging for any signs of growth that would require surgery.

Pitfall

- Mass effect on the posterior pituitary may cause diabetes insipidus which would need to be managed prior to undergoing surgery [42].

Pituitary Apoplexy

Pituitary apoplexy occurs in macroadenomas that have acute infarction or hemorrhage (Fig. 4.8). Appropriate management requires urgent administration of stress-dose steroids, pain control, and fluids. Surgical decompression of the pituitary is warranted in patients that show cranial nerve deficits [4, 26, 43, 44].

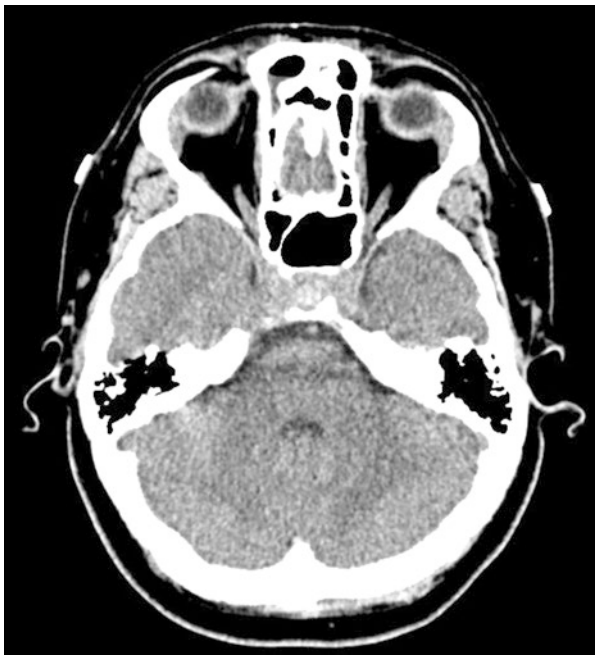

Fig. 4.8 Hemorrhage within a pituitary tumor consistent with pituitary apoplexy

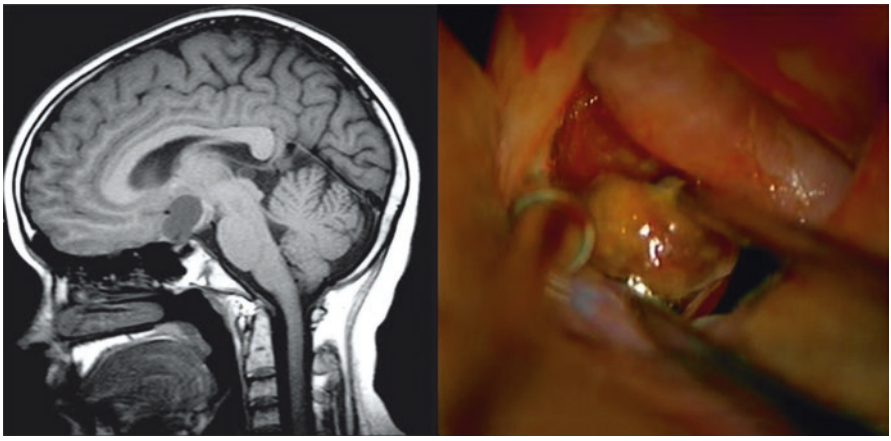

Fig. 4.9 *Left*, MRI of a craniopharyngioma with suprasellar cystic and solid mass, compatible with craniopharyngioma, (*right*) intraoperative view of the craniopharyngioma

Craniopharyngiomas

For craniopharyngiomas, most patients with this lesion require surgery from an intracranial approach to access the tumor given their growth at the pituitary stalk (Fig. 4.9). Some craniopharyngiomas that have large cystic components that extend down to the sella can be accessed with a transsphenoidal approach. Often, the tumors adhere to the undersurface of the optic chiasm or third ventricle making complete resection difficult. Many patients will require radiation following incomplete removal of this tumor [4].

Meningiomas

Meningiomas in the pituitary region are benign tumors that can be conservatively followed if it is not growing or causing any symptoms (Fig. 4.10). Once growth is observed on serial imaging, or symptoms result from tumor compression on nearby structures, then surgery could be pursued for decompression. For meningiomas that arise from the dura of the cavernous sinus, radiation therapy is used without a biopsy, as radiation has been shown to be effective at controlling tumor growth [4].

Infundibular/Hypothalamic Tumors

Lesions involving the pituitary stalk or hypothalamus cause hypopituitarism and will require an intracranial surgical approach. Surgery should be pursued for lesions that are symptomatic or suspected to be malignant. Smaller lesions on the pituitary stalk are often incidentally found, hardly ever grow, and can be conservatively managed [4].

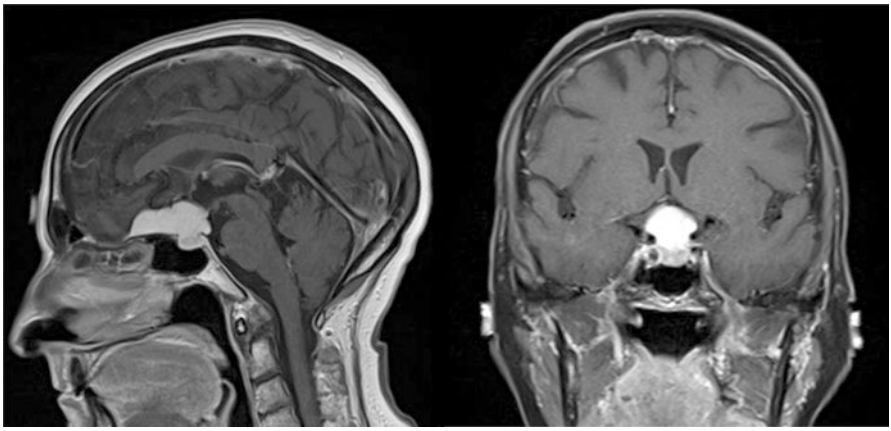

Fig. 4.10 Sellar meningioma extending along the planum sphenoidale

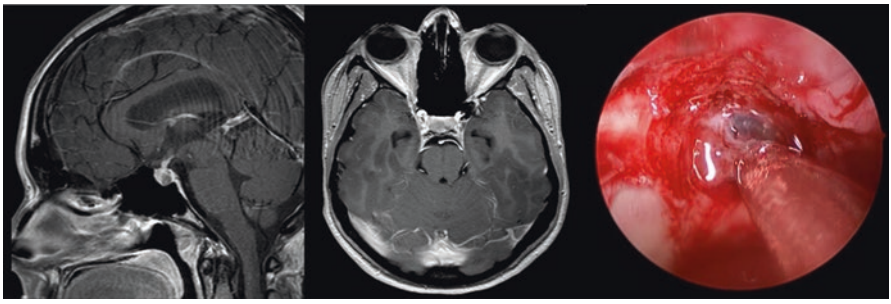

Fig. 4.11 Non-enhancing lesion in the sella turcica between the anterior and posterior pituitary glands representing a Rathke's cleft cyst in the (*left*) sagittal, (*middle*) axial, and (*right*) intraoperative transsphenoidal view

Cysts

Cysts can often present within the sella (Fig. 4.11). If the cysts are small with normal pituitary function, then they should be followed with an MRI. If these lesions begin to grow or start to cause symptoms, then surgery is an effective method to drain the cyst [4].

Metastasis

Metastatic disease in the sella is a rare occurrence, but requires surgery if the lesion is growing or causing symptoms. A transsphenoidal biopsy can be done to determine metastatic malignant disease. Once diagnosis is established, surgery can stop and adjuvant therapy can be pursued [4].

Reoperations

Reoperations on pituitary tumors require case by case considerations. If the tumor was not fully resected as a result of fibrotic consistency, invasiveness, or vascularity, additional surgery is unlikely to produce improved results and could result in worsening outcome [4]. Small recurrence of nonfunctional adenomas often can be treated with radiation, while larger recurrence that causes symptoms will require additional surgery before radiation [45]. If medical and radiation therapy fail to control an adenoma regarding symptomatic progression, surgical resection would be recommended [46–48]. Failed surgery or recurrence for Cushing's disease will require repeat surgery. Recurrence of acromegaly, however, can be treated with medical and radiation therapy [4].

Conclusion

Preoperative management of pituitary tumor patients requires the collaboration of multiple specialties, neurosurgery, endocrinology, and neuro-ophthalmology, in order to determine candidates for operative resections. Many types of tumors can present in the pituitary region and require careful analysis to determine whether surgery is appropriate and avoid pitfalls of operative planning.

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The Perioperative and Postoperative Care for Pituitary Patients

5

Saira Khan and Roberto Salvatori

Introduction

According to the Central Brain Tumor Registry of the United States, pituitary tumors are the second most common brain pathology seen [1]. Although prolactinomas are usually treated medically, the remaining pituitary adenomas and sellar and parasellar masses such as craniopharyngiomas, Rathke's cleft cysts, meningiomas, and less common tumors are treated surgically, with the majority of cases performed via the transsphenoidal approach. If a decision is made to pursue surgery, postoperative care by a multidisciplinary team including neurosurgery, endocrinology, and neuro-intensivists is a crucial component of the management [2].

In this chapter, we will begin by detailing key components of the preoperative assessment of pituitary patients. We will then focus on recognizing and managing the two most common postoperative problems after pituitary surgery: disorders of water balance and adrenal insufficiency. Finally, we will discuss the special postoperative management of patients with cortisol excess secondary to Cushing's disease.

Preoperative Hormonal Analysis

Awareness of a patient's preoperative hormonal status is a key component when planning the perioperative care. A careful physical examination and history should attempt to identify any evidence of hormone hypersecretion or deficiency.

S. Khan, MD • R. Salvatori, MD (✉)
Division of Endocrinology, Department of Medicine, and Pituitary Center,
Johns Hopkins University School of Medicine, 1830 East Monument Street #333
Baltimore 21287, MD, USA
e-mail: salvator@jhmi.edu

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_5

Routine baseline bloodwork includes measurement of prolactin, IGF-1 as a marker for possible growth hormone excess, and cortisol level [2]. Prolactin measurement is imperative, because prolactinomas are most often treated medically with dopamine agonist therapy, rather than surgically, even in the presence of optic chiasm compression. It is important to note, however, that prolactin elevation can sometimes be caused by stalk compression from a non-secreting sellar mass rather than a true prolactinoma. The degree of elevation in prolactin, usually greater than 200 ng/mL for macroprolactinomas, can often help distinguish prolactin-secreting adenomas from stalk effect. Furthermore, for patients with very large tumors (>4 cm in diameter) but minimal elevations in prolactin, serial diluted measurements of prolactin should be done to rule out the "hook effect," which may cause falsely low prolactin reading caused by extremely high prolactin overwhelming the "sandwich" assay [3, 4]. If there is concern about Cushing's disease, testing is performed to confirm cortisol excess via bedtime salivary cortisol testing, 24-h urine free cortisol measurement, and/or overnight dexamethasone suppression testing. At least two positive methods of testing are required to confirm cortisol excess. It is important to identify ACTH-producing pituitary adenomas in the preoperative setting, so that surgery can be planned to attempt complete resection and to predict postoperative adrenal insufficiency [5]. Notably, the degree of hypercortisolism does not necessarily correlate with the size of the mass, and therefore Cushing's disease should be suspected even if the clinical picture of hypercortisolism is mild in the presence of a large mass [6]. We will discuss the postoperative management of ACTH-producing adenomas in more detail later in this chapter.

In addition to hormonal hypersecretion, it is important to identify any hormonal deficiency prior to surgery. The most crucial of these is secondary adrenal insufficiency, which can be caused by mass effect from large sellar or parasellar lesions. One should begin with measurement of a fasting 8 AM serum cortisol level; if this is greater than 14 mcg/dL, adrenal insufficiency can effectively be ruled out. If it is <3 mcg/dl, adrenal insufficiency is present. For levels between 3.1 and 14 mcg/dL, it is prudent to perform a 250 mcg ACTH stimulation test, with rise of cortisol to greater than 20 mcg/dl (550 nm) at 30 or 60 min indicating an intact hypophyseal-pituitary-adrenal axis [7]. If a peak appropriate cortisol level is not achieved, perioperative stress dose steroids are recommended.

Other pituitary hormonal deficiencies may be present preoperatively. Measurement of free T4 should be performed and central hypothyroidism should be corrected prior to surgery, if feasible. Perioperative risks associated with severe hypothyroidism include cardiac dysfunction, hyponatremia, and postoperative ileus [8, 9]. Of note, all patients found to have central hypothyroidism should be evaluated for adrenal insufficiency prior to initiation of thyroid hormone replacement, to prevent precipitation of adrenal crisis. In patients with preoperative hypogonadism and growth hormone deficiency, treatment is typically deferred as these axes may recover after surgery and lack of correction does not affect the surgical outcome [2].

Disorders of Water Metabolism: Diabetes Insipidus and SIADH

The presence of preoperative diabetes insipidus (DI) should trigger suspicion for non-adenomatous masses, such as craniopharyngioma, or infiltrative or infectious causes (lymphocytic hypophysitis, sarcoidosis, tuberculosis, etc.). Indeed, DI occurs as a presenting symptom in approximately 15% of cases of craniopharyngioma, related to tumor effects on the pituitary stalk [10]. Preoperative DI is a very uncommon presentation of pituitary adenomas because the slow growth of the adenoma can allow for adaptation of neurohypophyseal function and development of new routes for antidiuretic hormone (ADH, also known as vasopressin) delivery [11]. Indeed, a shift in the site of ADH production from the posterior pituitary to the median eminence can sometimes be detected as an upward migration of the posterior bright spot on MRI [12]. Such patients can be less susceptible to DI from stalk manipulation during pituitary surgery [13].

Abnormalities of ADH secretion are the most common hormonal complication of pituitary surgery [14]. We will begin by reviewing the normal mechanisms of water metabolism. Thereafter, we will discuss the incidence, diagnosis, clinical course, and treatment of DI and SIADH.

Under normal circumstances, plasma osmolality is controlled by the secretion of ADH and by the thirst center in the cerebral cortex [15]. ADH is synthesized in the neurohypophyseal magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus. After synthesis, the ADH prohormone is packaged into neurosecretory granules that are transported down the pituitary stalk to be stored in the posterior pituitary. During this transport, the prohormone is enzymatically cleaved into ADH, neurophysin, and a C-terminal glycopeptide. Once released, ADH acts by binding to V2 receptors in the renal collecting duct, thereby stimulating the insertion of Aquaporin-2 water channels into the apical membrane of collecting duct epithelial cells that allow passive reabsorption of water from the renal medulla following osmotic gradients [16].

The stimuli for ADH release are two-fold. Baroreceptors in the carotid arteries and aortic arch are able to sense decreases in blood pressure and circulating volume, triggering release of ADH. A more powerful stimulus for ADH release is a change in plasma osmolality, with the osmotic threshold for ADH secretion usually set to greater than 282–285 milliosmole (mOsm)/kg H_2O. Osmoreceptors in the anterior hypothalamus are able to sense small changes in plasma osmolality, with changes of 1% or less triggering release of ADH and resultant increase in urine osmolality [12]. It is estimated that each 1 mOsm/kg H_2O increase in plasma osmolality causes an increase in plasma ADH level from 0.4 to 0.8 pg/mL [12]. Finally, factors other than baroreceptor or osmoreceptor stimulation can also trigger ADH release, including nausea, pain medications, angiotensin II, histamine, dopamine, bradykinin, and acetylcholine [17].

In the postoperative pituitary patient, disruptions in water balance can occur as a result of a decrease in ADH release leading to diabetes insipidus or excess ADH release leading to water retention and SIADH. In general, such disruptions in

water regulation can be linked to anatomic injury to the hypothalamus, pituitary stalk, or posterior pituitary gland during surgery. Studies have shown that, although transection of the pituitary stalk usually leads to permanent DI, resolution of DI can occur after distal dissections of the stalk [12].

Diabetes Insipidus

Incidence

DI occurs when there is a deficit of ADH action at the renal collecting duct, prohibiting the concentration of urine and resulting in large amounts of dilute urine output. DI can be central, due to decrease in ADH synthesis or release, or nephrogenic, secondary to ADH resistance at the level of the kidney. Central DI occurs when there is damage to the hypothalamic-posterior pituitary axis, either because of tumors, trauma, hemorrhage, thrombosis, infarction, granulomatous disease, or after pituitary surgery [12].

Postsurgical diabetes insipidus has been reported in up to 30% of pituitary surgical cases; however, the majority of these cases are transient [13]. Permanent DI has been reported in 0.5–15% of postoperative pituitary cases, less common because degeneration of more than 90% of the magnocellular ADH neurons in the supraoptic and paraventricular nuclei is required before permanent DI occurs [18]. Factors that confer a higher risk of permanent DI include craniopharyngiomas or Rathke's cleft cysts, microadenomas compared to macroadenomas, intraoperative CSF leak, and the neurosurgeon's expertise [19]. It is postulated that CSF leak may be a marker for more aggressive surgical resection, and microadenomas may require more extensive exploration and potential stalk manipulation in order to achieve complete resection [13]. Additionally, anatomic location of the lesion in reference to the hypothalamus also matters, with higher lesions conferring greater risk of permanent DI. In two studies, 62% of patients with pituitary stalk injury at the level of the diaphragm sellae developed permanent DI, compared to 80–100% of patients with higher levels of stalk injury [20, 21]. The presence of preoperative diabetes insipidus also confers a higher risk of permanent DI after surgery.

Diagnosis

The diagnosis of DI should be considered when a postoperative pituitary patient produces large amounts of dilute urine, typically exceeding 2.5 to 3.0 mL/kg body weight per hour [12]. The urine output usually exceeds 4–18 L/day and is hypotonic with urine specific gravity below 1.005 or urine osmolality below 200 mOsm/kg H_2O [14]. Onset of polyuria is usually abrupt, occurring within the first 24–48 h after surgery. The abrupt onset reflects a decrease in the number of functioning hypothalamic ADH-producing neurons by approximately 85–90%, after which

circulating ADH levels drop dramatically and polyuria ensues [18]. To screen for potential development of postoperative diabetes insipidus, we recommend measurement of urine output and fluid intake every 1–3 h, urine specific gravity daily, and serum sodium twice daily.

It is very important however to note that polyuria alone cannot define a diagnosis of DI, as there are several other circumstances that can lead to polyuria in the postoperative patient. Polyuria from osmotic diuresis can occur in the setting of hyperglycemia, especially in patients receiving glucocorticoids for secondary adrenal insufficiency. Therefore, one must be vigilant about monitoring for elevations in serum or urine glucose and attempt to achieve normoglycemia in order to eliminate osmotic diuresis as a potential cause of polyuria. Additionally, surgical patients often receive large amounts of intravenous fluids (IVF) in the perioperative period, leading to appropriate physiologic diuresis postoperatively. If such physiologic urine output is matched with additional administration of IVF, this could lead to subsequent hyponatremia, [12]. Finally, in patients with acromegaly, the abrupt decrease in growth hormone levels may cause significant increase in urine volume.

At this point, it is important to readdress the regulators of plasma osmolality, maintained not just by ADH action but also by the thirst center in the cerebral cortex. Thus, a key component in the diagnosis of DI is the onset of polydipsia, usually also within the first 24–48 h after surgery. Indeed, patients with postoperative DI often crave ice-cold water, which better satisfies the thirst mechanism [22]. With an intact thirst mechanism and uninhibited access to free water, patients with postoperative DI are usually able to maintain normal serum sodium levels. At our institution, as soon as it is safe to do so from an anesthesia standpoint, we place jugs of water and cups at the bedside, with nursing recording accurate intake and output and encouraging patients to drink according to thirst.

Postoperative Clinical Course of DI and Possible SIADH Phase

Postoperative DI can be transient or permanent, and in less than 5% of cases, the water balance picture appears to be triphasic [15]. In the cases of a triphasic response, there is an initial DI phase, followed by a phase of SIADH, finally leading again to DI that is often permanent. Anatomically, this can be explained by the pattern of intraoperative injury. The first phase of DI usually begins within 24–48 h postoperatively. This is related to dysfunction of ADH-producing neurons, from disrupted vascular supply to the magnocellular neurons of the hypothalamus, or severed connections between the hypothalamus and the posterior pituitary. If the ADH-producing neurons are able to recover, then the DI is transient. If the damage is more extensive, however, then degeneration of the neurons eventually leads to a dumping of existing ADH into circulation—precipitating the second phase, SIADH. This SIADH phase usually begins on postoperative day 5–7, and it lasts variably for 2–14 days [18]. To monitor for hyponatremia and SIADH, it is recommended to have a serum sodium level checked on postoperative day 5–8. Mild hyponatremia can be treated with fluid restriction, but more severe hyponatremia

(less than 125 mmol/L) warrants hospitalization for stricter fluid restriction and close sodium monitoring or, in the case of symptomatic altered mental status, use of hypertonic saline or ADH receptor antagonist drugs [2]. The one that can be used parenterally in the acute setting is Conivaptan, a competitive antagonist of ADH V1a and V2 receptors. A loading dose of 20 mg should be administered through a large vein over 30 min, followed by a maintenance dose of 20–40 mg per day for a maximum of 4 days. A more selective V2 oral preparation (Tolvaptan) is also available and is more suitable for long-term use. As postsurgical SIADH is usually self-limiting, the oral preparation is rarely needed [23].

As supplies of ADH are depleted in the posterior pituitary, and further synthesis of ADH is limited given damage in the hypothalamus, a third phase of permanent DI may ensue [12]. Although this triphasic picture is often cited, it is important to remember that all possible combinations can be seen, and the lack of transient DI does not mean that the patient has no risk for postoperative SIADH.

Finally, much less commonly than SIADH, hyponatremia after pituitary surgery may be caused by the cerebral salt wasting (CSW) syndrome. While SIADH is characterized by euvolemic hyponatremia (and thus treated optimally by fluid restriction), CSW is characterized by brain natriuretic peptide (BNP)-mediated hypovolemic hyponatremia (and thus managed with hypertonic fluid administration). The differential diagnosis between SIADH and the uncommon CSW syndrome is sometimes difficult. Weight (increased in SIADH and decreased in CSW), serum albumin, BUN, and hematocrit (normal or low in SIADH and increased in CSW) may help in the differential diagnosis [24].

Indications for Treatment in DI

Given its often transient course, it is important not to over-treat DI in the immediate postoperative period, to reduce the risk of precipitating hyponatremia if the second SIADH phase was to occur. As indicated above, patients with postoperative DI, who are awake, have intact thirst mechanisms, and free access to water can usually maintain normal serum sodium levels. At our institution, we follow a protocol for treatment for postoperative DI only if serum sodium rises greater than 145, in the context of dilute urine with specific gravity of 1.005 or less and urine output exceeding 250 cc/h or greater for three consecutive hours [25]. Additionally, for patients who are having bothersome polyuria overnight, treatment can be used for symptomatic control.

The mainstay of pharmacological treatment of DI in the immediate postoperative period is administration of subcutaneous ADH (vasopressin). Since DI is frequently transient, we recommend starting with single 5 IU doses, which are active for 2–6 h, and re-dose only if symptoms of diabetes insipidus persist. In cases of DI that persists past 48–72 h, longer-lasting formulations of ADH equivalent (1-desamino-8-D-arginine vasopressin-DDAVP, also called desmopressin, a synthetic ADH analog) can be initiated. Desmopressin is available as intranasal, oral, and (in some countries) sublingual melts forms. In the postoperative period, intranasal desmopressin is generally avoided, as nasal packing and the transsphenoidal approach of surgery

Table 5.1 Dose comparison of available DDAVP formulations

	Melts	Tablets	Spray	Injections
Dose equivalence	60 mcg 120 mcg 240 mcg	100 mcg 200 mcg 400 mcg	2.5 mcg 5.0 mcg 10.0 mcg	N.A. <0.5 mcg <1.0 mcg

N.A. not applicable [26]

can affect absorption of the medication. As such, oral desmopressin is usually administered at the lowest dose required to control symptoms, ranging from a single nocturnal dose of 0.2 mg at bedtime, to doses as high as 0.2 mg twice or three times a day, depending on severity of symptoms. If desmopressin is continued at discharge, it is imperative for the patient to refrain from re-dosing until symptoms of polyuria have recurred, to ensure that the DI is persistent [15]. In all forms, treatment must be monitored with great vigilance to prevent overdosing, which may result in hyponatremia. This is particularly important in elderly individuals, who may have increased renal sensitivity to the drug.

The non-injectable absorption of DDAVP is small. Oral and sublingual absorption rates are less than 1%, while intranasal is about 6% [26]. Most sprays deliver 10 mcg of desmopressin. A dose equivalence chart of different desmopressin formulations is presented in Table 5.1.

Recovery from DI may occur many weeks or even months after surgery. Therefore, we recommend that patients periodically (every couple of weeks) hold their desmopressin therapy during the 6 months after surgery to verify whether they continue to need it.

Adrenal Insufficiency

Patients with preoperative adrenal insufficiency should be started on replacement glucocorticoid therapy leading up to surgery and should receive stress dose steroids perioperatively. In the days leading up to surgery, we usually recommend hydrocortisone doses of 10–15 mg in the morning and 5–10 mg in the afternoon sometime between 3–5 pm. Studies have shown increased morbidity and mortality with use of higher replacement doses of glucocorticoid [27]. In the perioperative period, patients should receive stress dose steroids, usually 50 mg of intravenous hydrocortisone every 6-8 hours, with the first dose prior to the start of surgery. IV steroids should be tapered over the next 48 h, and thereafter baseline oral glucocorticoid dosing reinitiated, if the surgery and postoperative course are uncomplicated [7]. Studies in patients with normal HPA axis have shown that cortisol levels return to normal approximately 48 h after major surgery, thereby decreasing the need for longer postoperative steroid tapers [28].

The recommendations for perioperative glucocorticoid replacement are less clear in patients who have demonstrated intact HPA axis prior to surgery. The incidence of new adrenal insufficiency in patients with intact preoperative HPA axis has

been shown to range significantly, from 0.8% to 12% [29, 30]. Approaches to the perioperative care of such patients vary from empiric steroid dosing after surgery to steroid-sparing methods. At our institution, to avoid cases of delayed adrenal crisis in the postoperative period, we empirically place all patients on hydrocortisone 30 mg IV q8 hours for the first 24 h immediately after surgery, with rapid tapering to physiologic replacement dose of hydrocortisone 15–20 mg daily in 2 divided doses within the next 48 h. This oral hydrocortisone is continued until postoperative day 6 or 7, when (together with sodium) an 8 am cortisol is obtained (prior to the morning dose of hydrocortisone) to determine whether hydrocortisone needs to be continued. Cortisol values less than 5 mcg/dL suggest adrenal insufficiency and need for continued hydrocortisone administration, whereas values above 15 mcg/dL have low likelihood of adrenal insufficiency, allowing glucocorticoid discontinuation. Several studies have shown that ACTH stimulation testing can miss recent onset ACTH deficiency, and hence this test is not used in the postoperative period [28]. If glucocorticoids need to be continued based on a low POD 6 cortisol level, the HPA axis can be reassessed in 4–6 weeks with repeat 8 am cortisol measurement or ACTH stimulation testing at that time [7].

Several steroid-sparing approaches to perioperative management after pituitary surgery are also commonly used. In a recent study by Manuylova et al., 8 am POD 1 cortisol level could be used to identify patients with intact HPA axis, even with intraoperative use of dexamethasone for nausea, with glucocorticoid initiation only if POD1 cortisol level was less than 14 mcg/dL. HPA axis was also reassessed on POD-6, and glucocorticoids initiated if 8 am cortisol value was less than 14 mcg/dL. Using this approach, 67% of patients were found to have adequate morning cortisol levels on POD-1, none of whom went on to require glucocorticoid therapy on POD-6 or thereafter. Additionally, no adrenal crises occurred [31]. In a similar study by Inder et al., daily measurements of 8 am cortisol levels in the postoperative period were used as a guide for starting postoperative steroids. Patients with levels less than 3.6 mcg/dL were deemed likely adrenal insufficiency and started on glucocorticoid replacement, and levels between 3.6–16 mcg/dL were felt to be at risk for adrenal insufficiency and also received steroids. However, 8 am cortisol levels above 16 mcg/dL were felt unlikely to represent adrenal insufficiency, and these patients were not started on postoperative glucocorticoid replacement [7]. Similarly, Marko et al. found that an immediate postoperative day-of-surgery cortisol level (drawn 60–180 min after cessation of the operation) could predict HPA axis function, with values greater than or equal to 15 mcg/dL predicting intact function with 98% sensitivity, 97% accuracy, and 99% positive predictive value [32].

Although no approach has been proven to be superior, the choice of the approach must consider the expertise of the staff taking care of postoperative pituitary patients and the turnaround time for serum cortisol measurement in each institution.

Special Considerations in Patients with Cushing's Disease

In patients with Cushing's disease, normal corticotrophs are suppressed due to chronic cortisol hypersecretion caused by the ACTH-secreting adenoma. Thus, when complete surgical resection is successful, these patients will almost invariably become adrenally insufficient. Although there is no universally accepted definition of remission, postoperative cortisol values of less than 2 mcg/dL on POD1 have a less than 10% risk of recurrence in ten years [5]. On the other hand, if postoperative cortisol values do not drop below 5 mcg/dL, these patients are felt to have persistent disease, and plans should be made for repeat surgery, adjuvant radiation, or medical therapy as indicated [33]. Some centers administer postoperative glucocorticoid therapy to all Cushing's patients (assuming cure), posponing determination of whether cure was achieved to a later phase. Some practitioners however favor withholding empiric glucocorticoid replacement until proof of postoperative remission, with cortisol level less than 2–5 mcg/dL, has been documented. Although this may confer higher risk of adrenal crisis, in the appropriately monitored setting, it may aid in planning future therapies. Thus, an alternative approach of measuring serum cortisol every 6 h, and initiating glucocorticoid therapy only when levels drop below 2–5 mcg/dL, has also been described [34].

As far as dosing of postoperative steroids in patients with Cushing's disease, given their chronic state of hypercortisolism, some patients may develop postoperative steroid withdrawal syndrome even on physiologic replacement doses of glucocorticoid. Symptoms can include anorexia, nausea, weight loss, fatigue, myalgia, and lethargy. The pathophysiology of steroid withdrawal syndrome is unknown; however, patients may benefit from temporary increases in glucocorticoid dose and slower tapers down to physiologic doses [5].

Long-term follow-up of Cushing's disease patients who develop postoperative adrenal insufficiency includes reassessment of HPA axis at 2-3 month intervals to assess for recovery of endogenous function (or recurrence). This usually involves morning cortisol measurement and possibly subsequent ACTH stimulation testing, with values greater than 18 mcg/dL indicating axis recovery [5]. Typically, the first evidence of awakening of the HPA axis is an increase in plasma ACTH, which may occur several weeks or months before a rause in serum cortisol.

Conclusions

The postoperative management of patients undergoing transsphenoidal pituitary surgery requires a multidisciplinary approach among neurosurgery, endocrinology, and often intensive care teams. Knowledge of a patient's preoperative hormonal status will help guide management decisions in the perioperative period. The most common complications of electrolyte abnormalities related to DI or SIADH as well as adrenal insufficiency should be monitored and recognized and plans made for both immediate and long-term management.

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Neuro-ophthalmology of Pituitary Tumors

6

Robert M. Mallery and Sashank Prasad

The optic nerves, chiasm, and tracts lie within close proximity to the pituitary gland and sella, making vision loss a common complication of sellar region tumors. Temporal or bitemporal visual field loss, especially when associated with endocrinopathy, is highly suggestive of a pituitary tumor. Vision loss typically occurs insidiously due to the slow growth of most sellar tumors and may remain unrecognized until visual field loss is advanced. Acute vision loss can occur in some instances, such as with pituitary apoplexy. Rarely, sellar masses may also extend laterally to invade the cavernous sinuses and produce double vision owing to ocular motor neuropathies.

A neuro-ophthalmic evaluation including perimetric assessment of visual fields, evaluation for ocular motor nerve palsies, and fundus examination to detect evidence of optic neuropathy is essential for preoperative assessment and subsequent monitoring of all patients with sellar masses in close proximity to or compressing the optic nerves, chiasm, or optic tracts. Optical coherence tomography (OCT), which uses near-infrared light to produce extremely high-resolution cross-sectional images of the retina, can quantify the degree of optic nerve axonal loss, and OCT has become an important part of clinical care.

R.M. Mallery, MD (✉) • S. Prasad, MD
Division of Neuro-Ophthalmology, Department of Neurology, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA
e-mail: RMALLERY@BWH.HARVARD.EDU

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_6

Neuro-anatomy of the Optic Chiasm and Relation to Visual Symptoms

The optic nerves are formed by the retinal ganglion cell (RGC) axons and project posteromedially to join at the optic chiasm. Axons originating from RGCs in the nasal retina represent the temporal visual field and decussate in the optic chiasm to join axons from the temporal RGCs of the contralateral eye and form the optic tracts (Fig. 6.1, left). Hence, lesions of the orbital or intracranial optic nerve result in monocular visual loss, lesions of the optic chiasm result in bitemporal

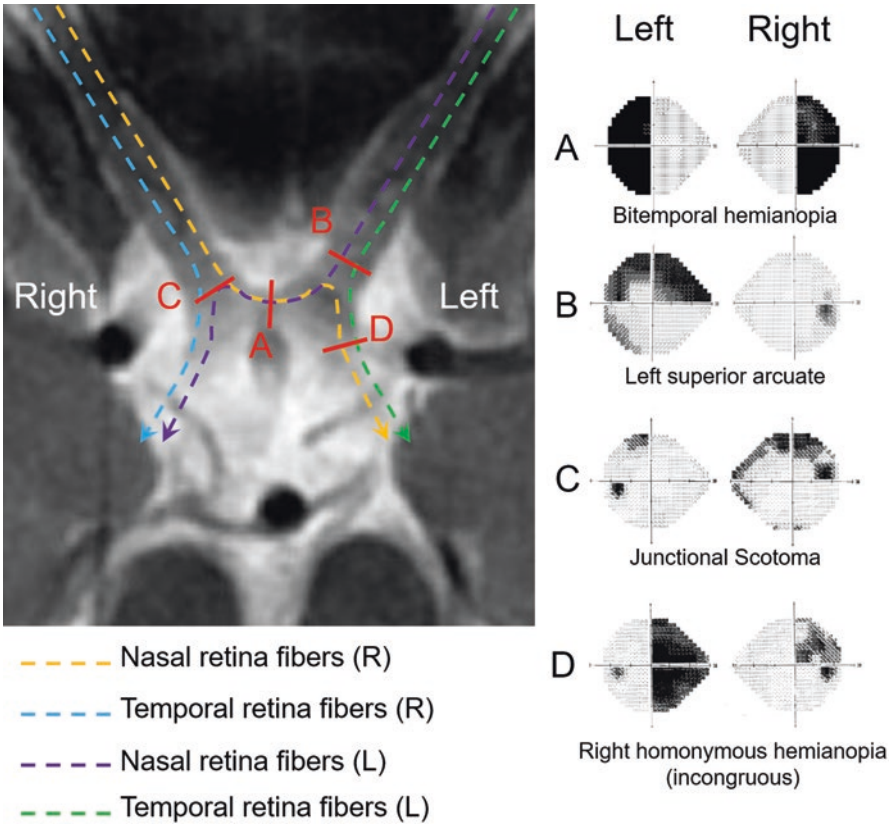

Fig. 6.1 Schema showing nasal fibers from each retina decussating in the optic chiasm. (*A*) A lesion in the central chiasm involves crossing nasal fibers from each eye, resulting in a bitemporal hemianopia. (*B*) A lesion of the pre-chiasmatic left optic nerve affects nasal and temporal fibers of the left eye, resulting in a superior arcuate defect in the left eye only. (*C*) A lesion at the junction of the optic chiasm and pre-chiasmatic right optic nerve involves nasal and temporal retinal fibers from the right eye and crossing nasal retinal fibers from the left eye, producing a junctional scotoma consisting of arcuate defect in the right eye and a superior-temporal defect in the left eye. (*D*) A lesion affecting the left optic tract resulting in an incongruous right homonymous hemianopia

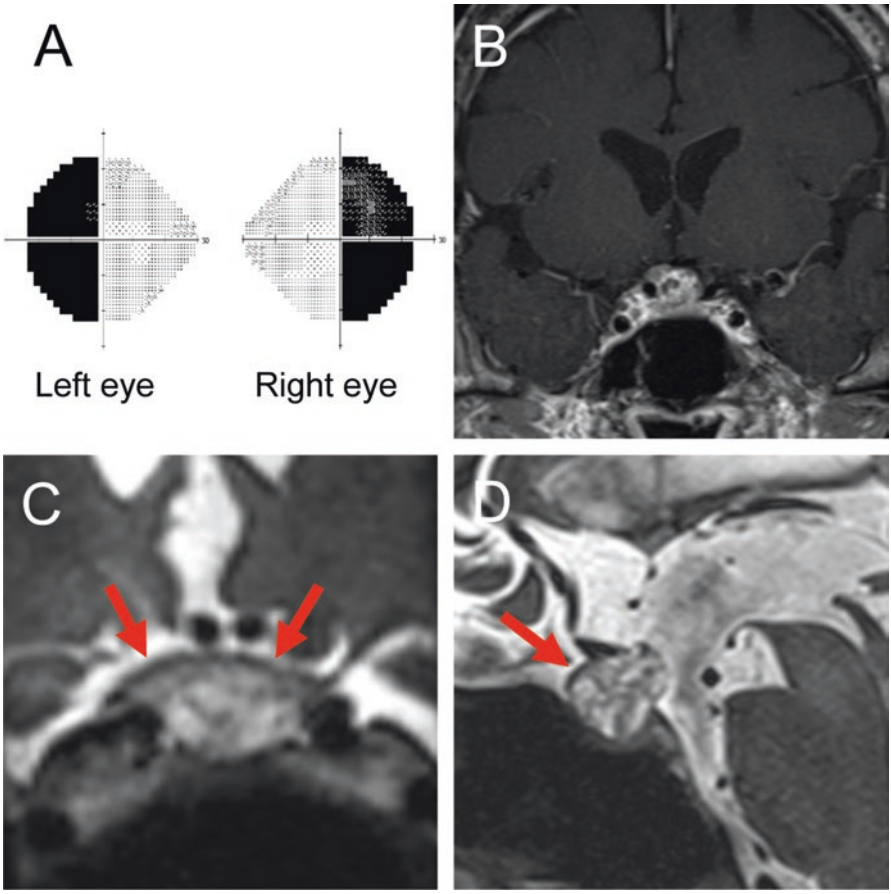

Fig. 6.2 Intrasellar craniopharyngioma causing vertical displacement of the optic chiasm. (**a**) Automated perimetry shows bitemporal hemianopia. (**b**) Coronal post-contrast T1-weighted MRI showing a heterogeneous lesion within the sella extending upward toward the optic chiasm and laterally toward the cavernous sinus. (**c**) and (**d**) Coronal and sagittal T2-weighted MRI showing vertical displacement of the optic chiasm (indicated by *red arrows*)

hemianopia, and lesions of the optic tract result in contralateral homonymous visual field loss (occurring on the same side of the vertical meridian in each eye) (Fig. 6.1, right). The optic chiasm is located in the suprasellar cistern, approximately 10 mm directly above the pituitary gland in most patients, making it vulnerable to compression by sellar lesions (Fig. 6.2). Visual symptoms may occur earlier in patients with a chiasm that is located closer to the tuberculum sella [6]. In addition, variations exist where the optic chiasm is prefixed (15% of patients) or postfixed (5% of patients) and the relative position of the chiasm influences whether pituitary lesions produce optic neuropathy, optic chiasmopathy, optic tract lesion, or a combination.

The Neuro-ophthalmic Examination

Snellen visual acuities, the pupillary light reflex, color vision, and visual fields are the basic components of the neuro-ophthalmic examination that allow localization of a lesion affecting the optic nerve, chiasm, or tract. Confrontation visual fields can be performed readily in clinic or at the bedside and, while less sensitive than formal perimetry (discussed below), are an important screening test and assist in localization. The examiner sits across from the patient who has one eye occluded. While the patient fixates on the examiner's nose, the visual field is tested by asking the patient to count fingers shown in each of the four quadrants. Reduced ability to count fingers in a given quadrant suggests at least a moderate degree of visual field loss. Unilateral visual field loss that involves central vision or both nasal and temporal quadrants suggests an optic neuropathy. Unilateral temporal or bitemporal visual field defects suggest a chiasmal process, and homonymous visual field deficits suggest a retrochiasmal lesion. Homonymous hemianopia due to an optic tract lesion is characteristically incongruous between the two eyes, meaning that the extent of vision loss is greater in one eye than the other. This pattern occurs because RGC axons encoding corresponding visual information from each eye are still separated within the optic tract; more posteriorly in the visual pathway, paired axons from each eye are closely juxtaposed.

A reduction in visual acuity, reduction in color vision (dyschromatopsia), or a relative afferent pupillary defect (RAPD) suggests optic neuropathy from compression of the prechiasmal optic nerve. Visual acuity is best assessed using a distance eye chart (most commonly a standard Snellen chart) rather than a near card to avoid the effect of impaired accommodation related to presbyopia and ensure reproducibility of the test distance during subsequent visits. The best-corrected visual acuity should be measured by testing visual acuity with the patient wearing their distance spectacles and using either a pinhole occluder or manual refraction to minimize any additional refractive error. When only near visual acuity can be tested, for example, in a patient on the surgical ward who is unable to be evaluated in clinic, presbyopic patients (over age 40) should be tested wearing their reading glasses or bifocals, and the near card should be held at 14 inches. Errors in near visual acuity testing typically arise from inadequate correction of presbyopia and the near card not being held at the standard 14 inch test distance.

Color vision is typically assessed using standard pseudoisochromatic Ishihara or Hardy-Rand-Rittler color plates. Patients are asked to identify numbers or shapes within an image of multicolored dots, and the result is scored as a fraction of the total plates tested. While pseudoisochromatic plates were initially designed to screen for congenital dyschromatopsia, acquired dyschromatopsia can suggest an optic neuropathy. Lesions affecting the optic chiasm may result in particular patterns of errors in color plate testing. Patients with macular-splitting temporal hemianopia may appear to have difficulty identifying color plates, but careful observation discloses that color discrimination is not impaired, and the patient is consistently failing to identify the portion of the numeral that falls temporal to the point of visual fixation.

A RAPD signifies asymmetric impairment of the signal transmitted by the retinal ganglion cell axons (optic nerve) of each eye. While a RAPD can occur with extensive retinal disease (such as a central retinal artery occlusion), it most commonly

signifies an optic neuropathy. The majority of sensory fibers that govern the pupillary light reflex arise from melanopsin-sensitive retinal ganglion cells, partially decussate in the optic chiasm, and project to the mesencephalic pretectal nuclei (PTN). Interneurons from the PTN connect to the bilateral Edinger-Westphal nuclei and drive the parasympathetic pupillomotor fibers of the third cranial nerves. Because of the bilateral projection of retinal ganglion cell axons to the PTN, a light shone in one eye results in bilateral and equal constriction of the pupils. If one optic nerve is asymmetrically affected, the pupils will partially dilate during the swinging flashlight test when a light is moved from the better eye to the eye that is more affected. A RAPD related to optic neuropathy is typically, but not always, accompanied by a reduction in visual acuity.

A RAPD can also help localize lesions to the optic tract. Optic tract compression is characterized by normal visual acuities, normal color vision, and a homonymous hemianopia on the contralateral side. A relative afferent pupillary defect can be present due to an asymmetry in the proportion of crossed and uncrossed fibers within the optic tract. Histological analysis of a human cadaver suggested a ratio of 53% crossed and 47% uncrossed fibers [10], but large variations in the magnitude of relative afferent pupillary defect in patients with complete optic tract lesions suggest that the percentage of crossed fibers may reach 67% in some patients [9].

Visual acuities, color vision, and the pupillary light reflex may be normal in patients with a purely chiasmal syndrome because uncrossed temporal RGC axons are spared and central vision remains preserved. When pupillary fibers are symmetrically affected, a relative afferent pupillary defect will not be present.

A unique form of vision loss known as *postfixation blindness* occurs in patients with dense bitemporal visual field defects (Fig. 6.3). Affected patients present with

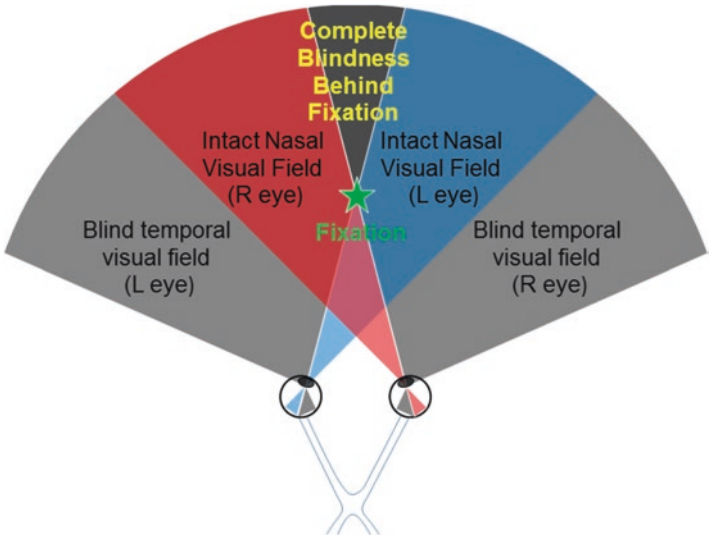

Fig. 6.3 Diagram showing postfixation blindness. In patients with complete bitemporal hemianopia, the area of binocular vision (overlapping nasal visual fields) lies in front of fixation, and points behind fixation are excluded from the visual field of either eye. Objects will disappear when they pass into this region

difficulty focusing on near targets because objects behind the fixation target lie in the blind temporal field of either eye and are not visible to the patient. Another unique visual symptom known as *hemifield slide* occurs in patients with dense bilateral temporal visual field loss who have an impaired ability to align the intact nasal visual field of each eye (Fig. 6.4). These patients complain of horizontal or vertical

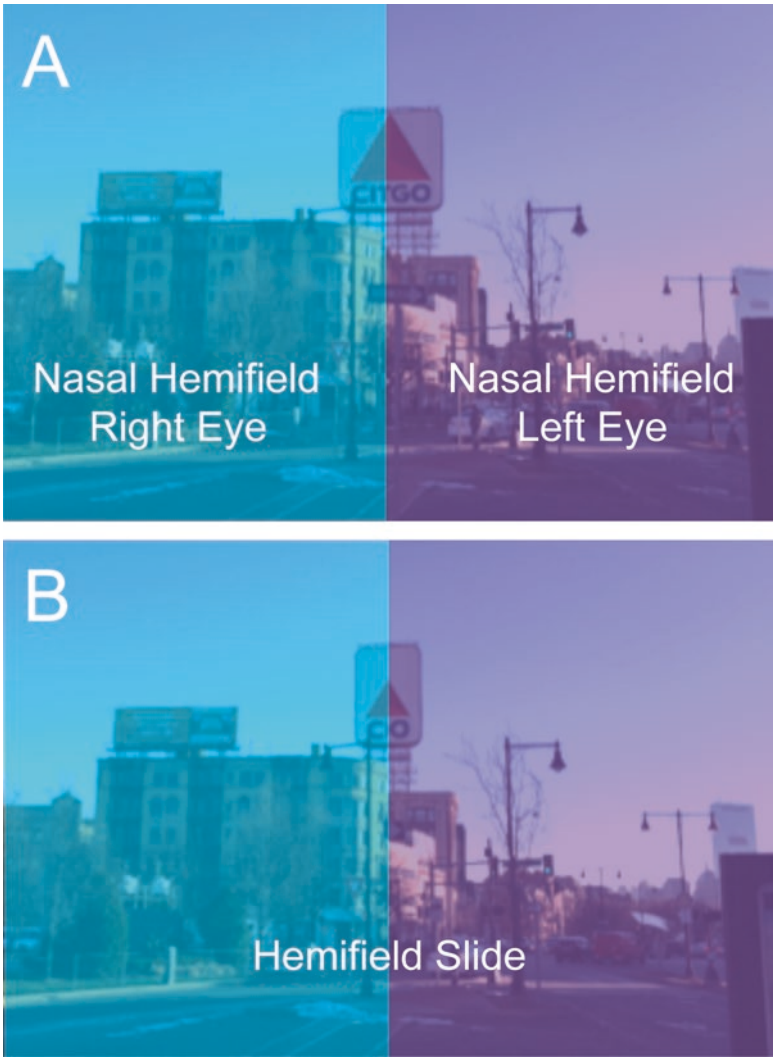

Fig. 6.4 Representation of the hemifield slide phenomena. (**a**) In patients with complete bitemporal hemianopia, the left side of vision is subserved by the nasal hemifield of the right eye, and the right side of vision is subserved by the nasal hemifield of the left eye. (**b**) In a patient with a tendency for the eyes to turn outward (exophoria), hemifield slide causes the nasal hemifields to move apart from each other, and objects straight ahead are no longer visually represented. In patients with a tendency for one eye to be higher (hyperphoria), the nasal hemifields may become vertically misaligned

slippage of the nasal visual fields due to either an inherent esophoria (tendency of the eyes to turn inward), exophoria (tendency of the eyes to turn outward), or hyperphoria (tendency for one eye to be higher).

Perimetric Assessment of the Visual Fields

Testing the visual field of each eye is the most sensitive measure to detect visual pathway compromise from sellar region tumors. Testing with automated static threshold perimetry is the most widely available method, offers an easily quantifiable measure, and does not require a trained perimetrist. During testing, the contralateral eye is occluded while the patient fixates on a central target within a calibrated perimetry bowl. Size III (~0.5°) visual stimuli are presented at varying intensity at each of the test locations within the perimeter. Standard test location patterns include 24–2 (54 points) and 30–2 (76 points) testing grids, which test the visual field within 24° and 30° of fixation, respectively, and have test points which straddle the horizontal and vertical meridians (Fig. 6.5a). Each visual field includes an assessment of visual field reliability, and a video-based pupil tracker assesses the quality of fixation. The detection threshold at each test point is determined by varying the light intensity until the patient detects the stimulus 50% of the time. Algorithms, such as the Swedish Interactive Thresholding Algorithm (SITA), speed up the efficiency of the test by taking into account the visual thresholds among neighboring points.

The visual field report includes multiple plots to assist in determining whether visual field loss is present, including plots of the threshold values (Fig. 6.5a), grayscale plot of threshold values (Fig. 6.5b), total deviation map (Fig. 6.5c), and pattern deviation plot (Fig. 6.5d). Of particular note are the total deviation plot and the pattern deviation plot. The total deviation plot assesses sensitivity difference (in dB) of each point from the age-normal threshold value. The pattern deviation plot takes into account the overall performance on the test to reduce noise due to generalized poor performance and can accentuate a nerve fiber bundle (related to optic nerve) or regional defects.

Goldmann manual perimetry requires a perimetrist to administer the test and is useful in uncooperative patients or in patients with more severely affected visual field. Goldmann perimetry is a form of kinetic perimetry where a patient detects a light stimulus moving in from the periphery. The test stimulus size and light intensity are varied to plot multiple isopters, similar to the creation of a topographical map. The isopters are named with a Roman numeral, Arabic numeral, and letter. The Roman numeral (I–V) represents the stimulus size (ranging from 1/16 to 64 mm^2), and the Arabic numeral and letter represent the degree of light attenuation. An example of a Goldmann visual field in a normal individual and in a patient with a pituitary macroadenoma compressing the optic chiasm is shown in Fig. 6.6.

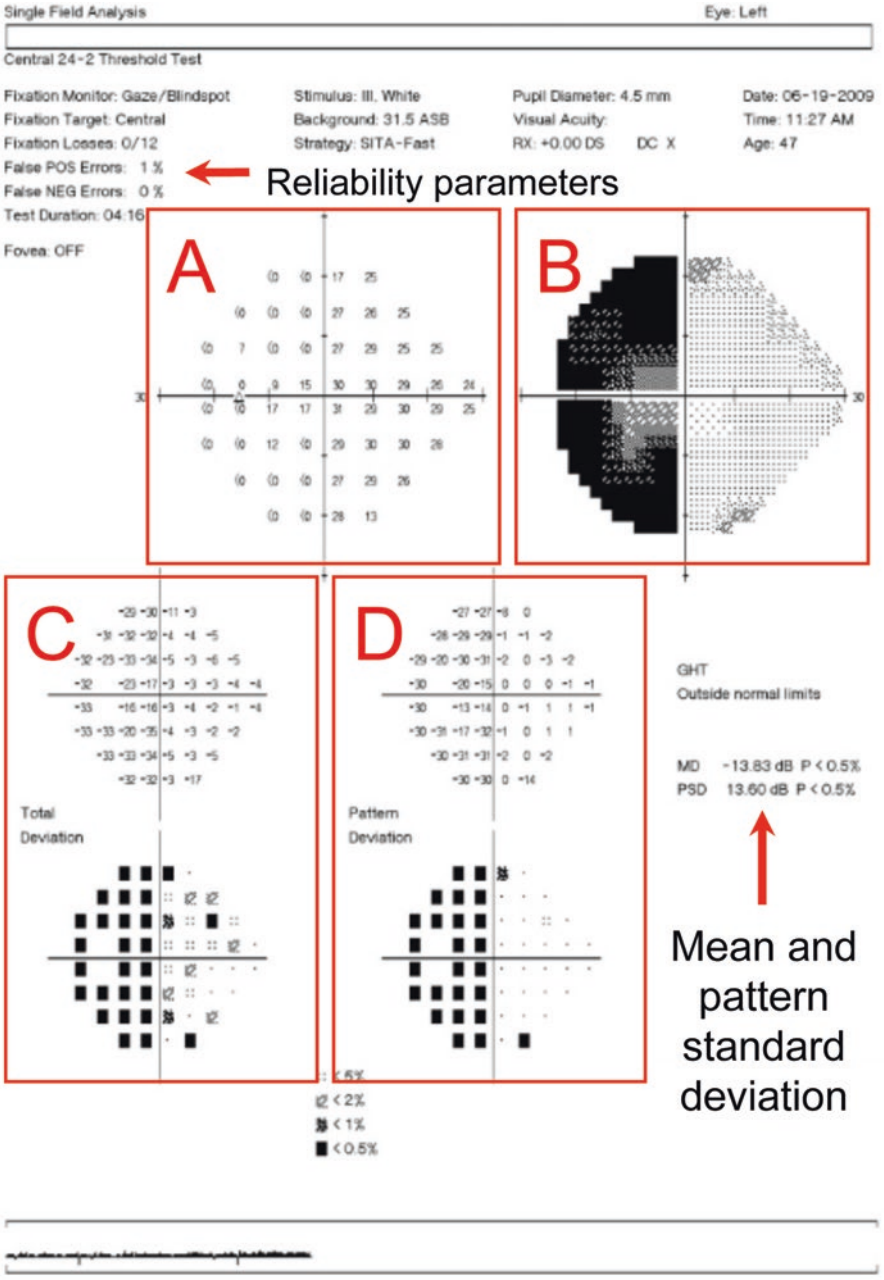

Fig. 6.5 Humphrey visual field report (24–2 SITA algorithm). (*A*) Visual detection threshold values (dB) for each location in the 24–2 testing grid. (*B*) Grayscale representation of the threshold values (dB). (*C*) Total deviation plot showing the deviation from age-matched controls (dB). (*D*) Pattern deviation plot controls for the overall reduction in sensitivity of the visual field and accentuates regional or nerve fiber bundle defects. In this example the temporal hemianopia more clearly respects the vertical meridian

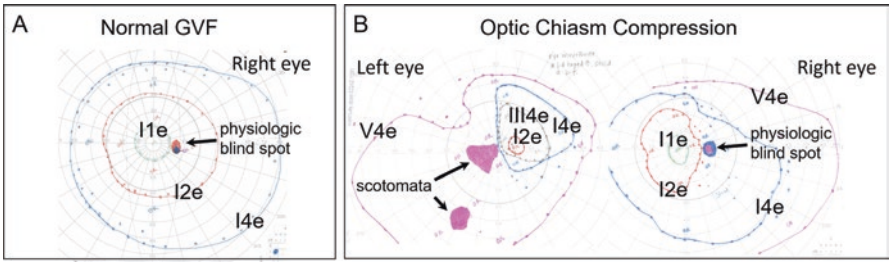

Fig. 6.6 Goldmann kinetic perimetry in a normal patient (**a**) and a patient with optic chiasm compression by a pituitary macroadenoma (**b**). The visual field is plotted as a series of isopters, each outlining the region where a stimulus of a given size and brightness was detected. The innermost isopter is the smallest, dimmest stimulus that was detected. The outer isopters are derived from larger, brighter stimuli. Filled in regions represent scotomata (**b**, left eye) or the physiologic blind spot (**b**, right eye). In this example the patient has temporal visual field constriction in the right eye and temporal and inferior-nasal loss in the left eye. The I4e (*blue*) isopter respects the vertical meridian, suggesting a chiasmal process

Patterns of Visual Field Loss

The pattern of visual field loss may vary depending upon the location of compression of the optic nerve or chiasm (Fig. 6.1). Compression of the body of the optic chiasm typically results in temporal or bitemporal hemianopia, while more anterior compression of the optic nerves can result in arcuate or central scotomas. A specific form of visual field defect known as a junctional scotoma occurs when there is compression at the junction of the intraorbital optic nerve and chiasm. Patients with junctional scotomas have an optic nerve-related visual field defect suggestive of optic neuropathy on the ipsilateral side of the lesion coupled with a supratemporal visual field defect in the contralateral eye due to involvement of crossing nasal fibers in Wilbrand's knee. Patients with a prefixed optic chiasm can present with an optic tract lesion and homonymous defects.

Structural Assessment of the Optic Pathways

Fundus Examination

Evaluation of the structural integrity of the optic pathways includes the fundus examination. Compression of the optic nerves, chiasm, or tracts can lead to loss of retinal ganglion cell axons that is evident as optic nerve pallor or atrophy. Optic disc cupping, mimicking glaucoma, may also occur due to chronic optic nerve compression. A specific pattern of optic atrophy, termed "band" or "bowtie" optic atrophy, occurs in patients with bitemporal hemianopia. Loss of RGCs nasal to the fovea and degeneration of their axons lead to temporal and nasal wedges of optic atrophy. The superior and inferior portions of the optic nerve are preserved, as these consist of

RGC axons from the temporal hemiretina. Temporal or diffuse optic disc pallor is also commonly seen. Once optic atrophy is visible, there has been significant loss of RGC axons, and vision may remain permanently compromised. Fundus photography to document the extent of visible optic atrophy or optic disc cupping may be helpful for monitoring changes over time. Visual field loss with normal-appearing optic nerves suggests conduction block along the RGC axons and a good prognosis for recovery of visual field following decompressive surgery.

Optical Coherence Tomography

Optical coherence tomography (OCT) is an imaging modality capable of assessing structural changes of the retinal nerve fiber layer (RNFL) or retinal ganglion cell layer (GCL) in patients with compressive lesions affecting the optic nerves or chiasm. OCT utilizes backscatter from near-infrared light (low coherence interferometry) to produce cross-sectional images of the retina. Retinal layers are distinguished by their degree of reflectivity, and automated segmentation techniques permit the calculation of the thickness of the RNFL surrounding the optic nerve head or the thickness of the ganglion cell layer within the macula (central retina). Newer generation spectral-domain OCT technology has high reproducibility due to advanced eye tracking technology and an axial resolution of 1–5 microns, making it highly suitable for measuring structural changes over time that are not visible by fundus examination alone.

Optic atrophy is evident on OCT as thinning of the peripapillary retinal nerve fiber layer (RNFL) and thinning of the GCL (Fig. 6.7). In patients with band optic atrophy, RNFL and macular GCL loss correlate spatially with the area of visual field loss [1, 11]. For example, patients with temporal hemianopia relating to chiasmal compression may show thinning of the GCL in the corresponding nasal macula on OCT (Fig. 6.7e, f). OCT may also have prognostic significance and offer a method to monitor for the progression of optic neuropathy in patients with known visual field loss who have not yet undergone surgery. In patients with pituitary adenomas compressing the optic chiasm, RNFL thinning on OCT suggests a decreased likelihood of full recovery following decompressive surgery [5, 8].

Management of Visual Loss

Visual field loss with or without optic nerve pallor or changes on OCT is typically an indication for surgery, except for prolactinomas where medical treatment with dopamine agonists (cabergoline or bromocriptine) may decrease tumor size and cause visual function to improve. Improvement in visual function occurs in approximately 80% of patients with vision loss undergoing transsphenoidal surgery for decompression of the optic chiasm, [3, 7, 12] and greater recovery is expected in

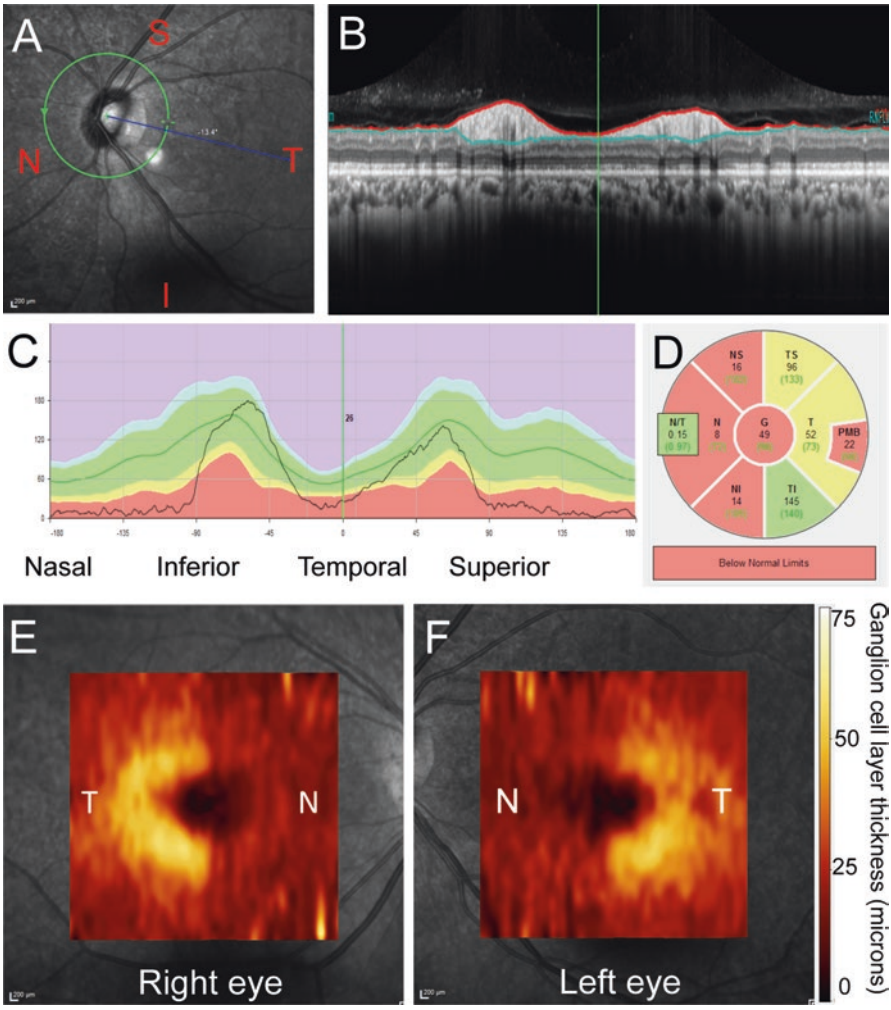

Fig. 6.7 Optical coherence tomography (OCT) of patient in Fig. 6.2 with bitemporal hemianopia related to optic chiasm compression from a craniopharyngioma. (**a**) Infrared scanning laser ophthalmoscope image showing the location of the circular OCT scan around the optic nerve. (**b**) B-scan (cross section) of the retina along the circle defined in (**a**). An automated image segmentation algorithm detects the internal limiting membrane (ILM, *red*) and the interface between the retinal nerve fiber layer (RNFL) and the ganglion cell layer (GCL) (*blue*). The RNFL is highly reflectant (*bright*). (**c**) Plot of the RNFL thickness compared with age-matched normal patients (*green*). (**d**) There is a total overall reduction in RNFL thickness which is most significant in the nasal portion of the disc and the papillomacular bundle. (**e**, **f**) GCL segmentation and thickness map plots show thinning of the GCL in the nasal macula of each eye, concordant with the presence of bitemporal hemianopia and loss of retinal ganglion cells with axons that decussate in the optic chiasm. **N nasal, T temporal, S superior, I inferior*

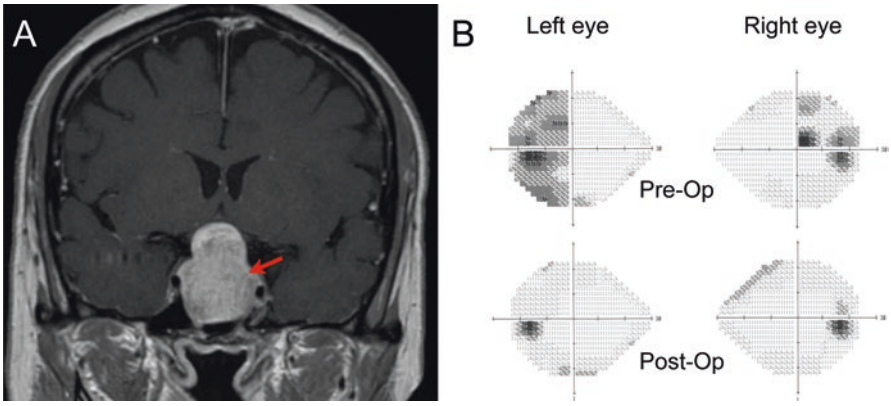

Fig. 6.8 Visual field improvement following transsphenoidal resection of a large pituitary macroadenoma in a patient with acromegaly. Fundus exam showed no evidence of optic atrophy. (**a**) Coronal post-contrast T1-weighted MRI showing a large macroadenoma (*arrow*) with upward displacement of the optic chiasm. (**b**) Preoperative automated perimetry showing bitemporal defects. The visual field sensitivities returned to normal following surgery

patients without optic nerve pallor or OCT changes (Fig. 6.8) [5, 8]. In patients with compression of the optic nerves or chiasm without visual field loss or symptoms, frequent monitoring of the visual fields and optic nerve structure is a reasonable alternative to surgery if there are no other neurologic or endocrinologic concerns. In this scenario, there are no formal guidelines for how often visual field testing should occur, but every 6 months is common practice.

Postoperative Visual Loss

Visual loss following transsphenoidal surgery is rare, occurring 0.6–2.6% of the time [4, 12]. The rate may be up to 5% in patients with vision loss prior to surgery [7], which likely reflects the increased complications associated with larger or more invasive tumors. Perioperative vision loss may occur from several different mechanisms, including direct trauma related to tumor removal, devascularization of the optic apparatus, compression by a postoperative hematoma, packing of the sella with excess fat or muscle, direct injury to the optic nerves from fracture of the optic foramen, prolapse of the optic chiasm or nerves into an empty sella, or cerebral vasospasm [2]. Prompt recognition of postoperative visual loss and imaging assessment for hematoma, excessive packing of the sella, or direct injury of the optic nerves by a bony fragment in the optic canal can identify a reversible cause. Rarely, prolapse of the optic chiasm into an empty sella may also occur in a delayed fashion months or years later and require chiasmapexy.

Efferent Neuro-ophthalmic Complications of Sellar Tumors

Large pituitary tumors may extend laterally into the cavernous sinus and cause an ocular motility disturbance [7, 13]. The third (oculomotor), fourth (trochlear), and sixth (abducens) cranial nerves, the ophthalmic (V1) and maxillary (V2) divisions of the fifth (trigeminal) cranial nerve, and the sympathetic pupillomotor fibers pass through the cavernous sinus (Fig. 6.9). Disruption of these nerves can give rise to ocular motility, eyelid, or pupil abnormalities. Patients reporting binocular double vision should have an assessment of ocular ductions (movements of each eye), ocular alignment, eyelids to identify ptosis, and pupil responses. Table 6.1 outlines the neuro-ophthalmic findings of cavernous sinus pathology.

Ocular motility disturbances are a common presenting feature of pituitary apoplexy (Fig. 6.10). Sudden vision loss or diplopia can occur with apoplexy of a large pituitary macroadenoma and represents an emergency due to the risk of hemodynamic instability related to adrenal insufficiency.

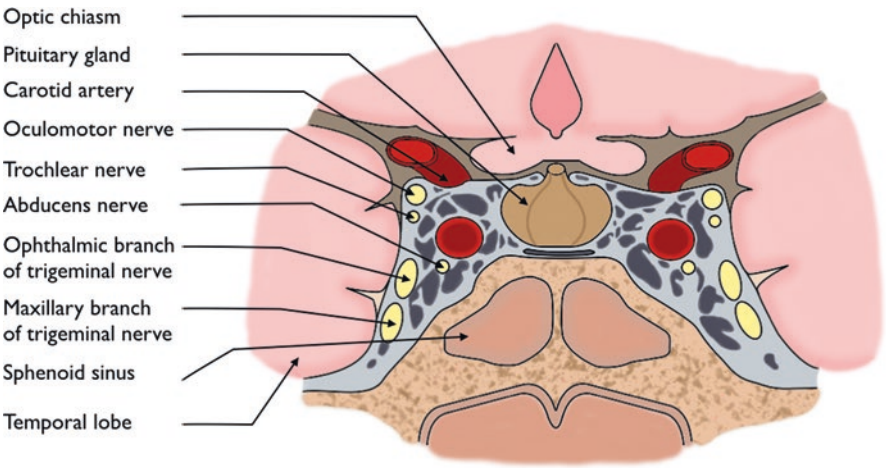

Fig. 6.9 Anatomy of the cavernous sinus. The ocular motor nerves (third, fourth, and sixth cranial nerves) lie within the cavernous sinus as they pass toward the superior orbital fissure. The sixth cranial nerve lies most medially, adjacent to the internal carotid artery, and the third and fourth cranial nerves lie against the lateral wall of the cavernous sinus. The ophthalmic (V1) and maxillary (V2) divisions of the fifth (trigeminal) cranial nerve also pass along the lateral margin of the cavernous sinus. Ocular sympathetic fibers also pass along the internal carotid artery. Combinations of ocular motor nerve palsies, facial numbness or pain, and Horner's syndrome could result if a pituitary tumor invades the cavernous sinus. Used with permission of Modern Neurology, LLC

Table 6.1 Neuro-ophthalmic findings of cavernous sinus lesions

Cavernous sinus structure	Symptoms	Neuro-ophthalmic findings
Third cranial n	Vertical or horizontal binocular diplopia (resolves with covering either eye) Impaired vision due to ptosis obscuring the pupil	Superior division: upper eyelid ptosis, impaired supraduction Inferior division: limited adduction or infraduction, pupil dilation (anisocoria greater in the light)
Fourth cranial n	Vertical binocular diplopia, greater looking away from the side of the lesion	Compensatory head tilt away from the side of the lesion Limited infraduction of the eye in the adducted position Vertical misalignment of the eye (hyperphoria or hypertropia), greater looking away from the lesion, down, and with head tilt toward the side of the lesion Excyclotorsion of the eye (visible as fundus rotation)
Sixth cranial n	Horizontal binocular diplopia, greater looking toward the side of the lesion and in the distance	Limited abduction of the eye Inward turning of the eyes (esophoria or esotropia), greater looking toward the side of the lesion
Oculosympathetics	Mild ptosis or anisocoria*	Horner's syndrome: anisocoria greater in the dark due to impaired pupil dilation Dilation lag Mild upper and lower eyelid ptosis (Mueller's muscle) *Anhidrosis is not a finding of Horner's syndrome from cavernous sinus involvement
Trigeminal n (V1 and V2)	Numbness in the V1 and V2 dermatomes Trigeminal neuralgia	Hypoesthesia (reduced sensation) in the V1 and V2 dermatomes Absent corneal blink reflex Corneal epithelial dysfunction

Special Considerations

In patients with pituitary tumors, other sources of vision loss should also be addressed fully, including refractive error, presbyopia, corneal abnormalities, cataract, and retinal disease. When vision loss occurs in both eyes and is severe, patients may be unable to drive which affects their sense of independence and quality of life. Psychological aspects of severe visual loss must also be addressed, and referral to a low vision specialist may provide important rehabilitative strategies. When ocular motility abnormalities produce persistent binocular diplopia that fails to resolve, a treatment strategy must be tailored to each patient. Options to alleviate diplopia include occlusion (by patch or with semitransparent tape), prisms placed on spectacle lenses, or in some cases corrective strabismus surgery.

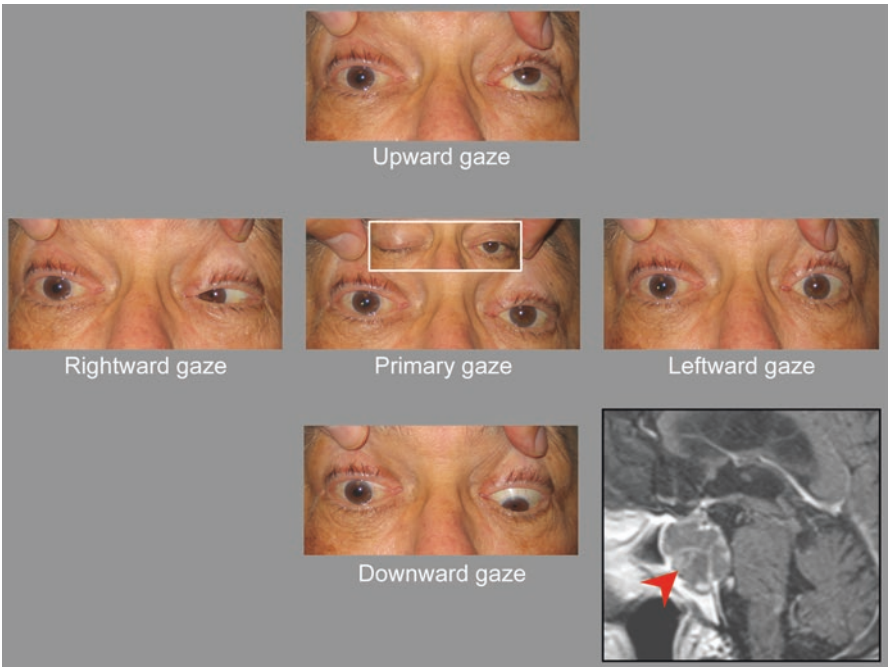

Fig. 6.10 75-year-old man with complex ophthalmoplegia related to pituitary apoplexy. There is complete right upper eyelid ptosis, dilation of the right pupil, and impaired elevation, depression, and adduction of the right eye, consistent with a right third nerve palsy. There is limited abduction of the right eye related to a right sixth nerve palsy. There is mild upper and lower eyelid ptosis and a miotic pupil on the left suggesting a left Horner's syndrome (oculosympathetic palsy). There is limited abduction of the left eye due to a left sixth nerve palsy. Sagittal T1-weighted MRI with contrast shows a large pituitary adenoma with internal signal hyperintensity and enhancement consistent with internal hemorrhage (*arrow head*)

Conclusion

Vision loss related to compression of the optic nerves, chiasm, or tracts is a common complication of pituitary tumors and a major symptom requiring surgical intervention. Less commonly, double vision can occur through involvement of the cavernous sinuses by tumor or as a result of pituitary apoplexy. A neuro-ophthalmic assessment is essential for quantifying the extent of vision loss, characterizing any disorder of ocular motility, monitoring for worsening of vision in cases of residual tumor, and assessing the response to transsphenoidal decompression.

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Rhinologic Evaluation of Patients Undergoing Transsphenoidal Surgery

7

Michael Freeman, Jose Gurrola II, and Spencer C. Payne

Historical Perspective

The first documented transsphenoidal approach to the pituitary gland was in 1907, when Hermann Schloffer introduced the transnasal transsphenoidal approach [1, 2]. Three years later, Harvey Cushing modified a translabial surgery created by Halsted and Kocher to pioneer the sublabial transsphenoidal approach to the pituitary [2, 3]. In the 1990s, the widespread adoption of rigid endoscopy allowed for microscopic sublabial approaches to be abandoned in favor of transcolumellar approaches without compromising retraction or surgical site visibility [4–8]. In the ensuing years, the sublabial and transcolumellar approaches have been found to have similar complication rates, but the endoscopic transnasal approach to transsphenoidal surgery has demonstrated superior surgical resection [7–9].

Prior to the advent of endoscopic transsphenoidal surgery, the role of otolaryngology was largely limited to outlining anatomic concerns regarding the sphenoid sinus. As endoscopy increasingly becomes the de facto approach to transsphenoidal surgery, obtaining a sufficient view of the operative field often justifies turbinectomy, septectomy, or septoplasty. As otorhinolaryngologists are experts in these procedures, both their assistance in the operating room and a thorough preoperative otorhinolaryngological evaluation have become relevant to transsphenoidal surgical outcomes.

M. Freeman
University of Virginia School of Medicine, Charlottesville, VA, USA

J. Gurrola II
Department of Otolaryngology, Head & Neck Surgery, University of Virginia School of Medicine, Charlottesville, VA, USA

S.C. Payne (✉)
Department of Otolaryngology, Head & Neck Surgery, Division of Allergy & Clinical Immunology, University of Virginia School of Medicine, Charlottesville, VA, USA
e-mail: SCP9X@hscmail.mcc.virginia.edu

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_7

Nasal Functions and Physiology

The nose primarily functions to humidify and warm incoming air, remove airborne particulates, engage the sense of smell, and allow unobstructed passage of air. The importance of these nasal functions is supported by quality of life assessments in patients with chronic nasal obstruction, nasal valve collapse, anosmia, and empty nose syndrome. The preservation of nasal structures and mucosa is important in maintaining nasal airflow and comfort. Otolaryngologists often assist in the approach to the sphenoid sinus to maximize exposure while limiting rhinologic complications.

Paranasal Sinus Function and Physiology

The exact function of the paranasal sinuses is uncertain. Some have theorized that, without the pneumatization of the facial skeleton that results in the formation of the sinuses, the weight of the head would be too great. However, given the large head to body size ratio of children, this postulate is less likely. Others have also suggested that the sinuses serve to insulate intracranial structures with air, similar to the properties of double-paned glass. In truth, the most widely accepted and putatively logical explanation of the sinuses is that they serve as a "crumple zone" and prevent transmission of force to the orbital and intracranial contents in the event of blunt trauma. This has been supported by the works of several authors [10, 11]. The mucosa of the nasal cavity and sinuses is the same pseudostratified columnar epithelium that lines the respiratory tract, but is ectodermally derived as opposed to endodermal derivatives of the lower airway. Replete with numerous serous and mucinous glands, the nasal cavity and paranasal sinuses produce about one liter of mucus daily. As such, iatrogenic obstruction of the sinus outflow tracts can be significantly detrimental to a patient's postoperative course and quality of life.

Preoperative Considerations/Workup

Preoperative evaluation should incorporate a careful medical and surgical history, physical examination including endoscopic assessment, and imaging studies. The absence of a bleeding disorder or an anticoagulant regimen should be verified. A history of sinonasal conditions such as chronic sinusitis, rhinitis, nasal polyps, or sinonasal neoplasms such as inverted papilloma is associated with narrowing or blocking of nasal passages and increased mucosal bleeding, impairing visibility. These conditions often necessitate more aggressive displacement or outright resection of tissue, which increases risk of complications. The presence of an active bacterial sinusitis should be medically treated with antibiotics prior to surgery to reduce the risk of infection tracking into the surgical site. It is also important to avoid nasal packing in cases of active sinusitis. If an otolaryngologist is present to assist with the approach, surgery for many sinonasal conditions can be performed concomitant to the approach for the transsphenoidal surgery. Nasal endoscopy is helpful in determining the severity of these conditions and is of heightened importance in patients

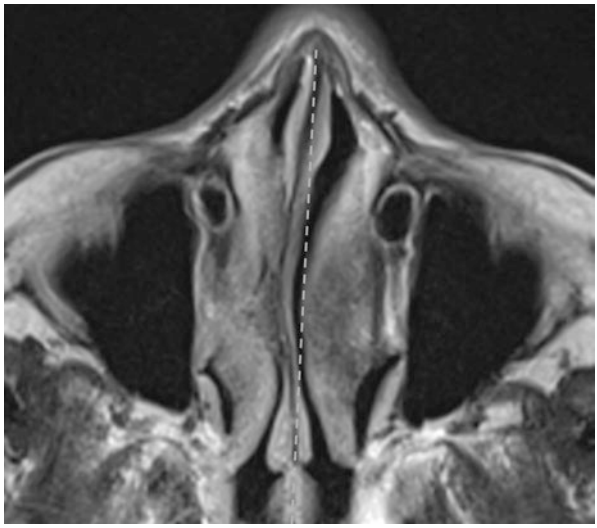

Fig. 7.1 Septal deviation. Often visible on axial MRI sequences. This image demonstrates deviation of the bony septum from midline (*dashed line*) with spurring to the patient's right side

complaining of recurrent infection, obstruction, congestion, rhinorrhea, postnasal drip, or recurrent epistaxis.

A detailed nasal surgical history must be elicited. Prior septoplasty or septorhinoplasty can cause scarring of the septum (especially with loss of quadrilateral cartilage) that complicates septal flap dissection and elevation. Prior nasal surgery can also leave synechiae (adhesions) that narrow and block nasal passages and obscure the approach to the sphenoid sinus.

Nasal anatomy should be evaluated at the preoperative workup, ideally via nasal endoscopy. The endoscopic view allows for visualization of posterior and anterior nasal deformities, whereas the nasal speculum examination is limited to the anterior nasal vault. This is paramount when intranasal surgery has already been performed, but it is less valuable in the absence of surgical history. Internal nasal anatomic variants can complicate the approach to the sphenoid, especially in the posterior nasal cavity. A common variant, especially contralateral to a concomitant septal deviation, is the pneumatization and enlargement of the middle turbinate. Termed a concha bullosa, the presence of this structure can complicate either the lateralization or resection of the middle turbinate during an endoscopic approach. Failure to recognize and address a concha bullosa may increase the probability of iatrogenic osteomeatal complex obstruction and subsequent sinusitis. Another common variant is the sphenoethmoidal (aka Onodi) air cells. These can be identified pathognomonically on coronal view radiologic images when horizontal septations are seen within the sphenoid sinus. A complete opening of the sphenoid and visualization of the sella can be significantly hampered if these cells are not addressed.

Septal deviation seen on preoperative workup can dictate the operative approach and justify/require intraoperative septoplasty (Fig. 7.1). Generally, spurs or significant deflections at the level of the lower portion of the middle turbinate will necessitate correction. Further, understanding the shape of a deviated septum can help in

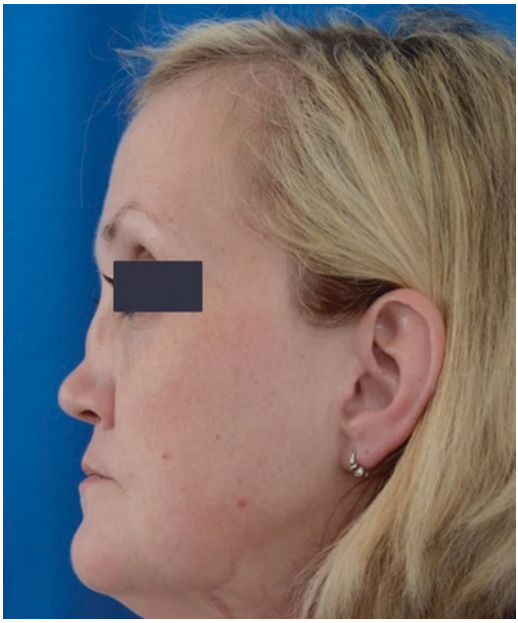

Fig. 7.2 Saddle nose deformity. This usually indicates a destructive process and likely lack of underlying cartilaginous septum. Further workup is necessary

planning for a nasoseptal flap elevation that may be required for skull base reconstruction. It is far easier to elevate a flap from the concave side of a septal deflection, but if that side also involves a septal spur, the dissection will be delicate and require significant skill to prevent incidental tearing. Septal perforation present before surgery can also pose a challenge. Depending on the location of the perforation, the maximal length or width of any planned mucosal flap may be diminished. Furthermore, if the surgical plan includes a posterior septectomy, as is the standard at the authors' institution, a significant increase in the size of the perforation and a change in nasal symptoms can occur. Risk factors for septal perforation should be elicited during the preoperative evaluation and include prior nasal trauma, prior septal surgery, intranasal cocaine use, and/or autoimmune conditions such as granulomatous polyangiitis (formerly Wegener's granulomatosis) or sarcoidosis.

Abnormalities of the nasal pyramid and tip support structures can also complicate the surgical approach to the sphenoid. Saddle nose deformity is a condition in which the support mechanisms of the external nose fail, resulting in collapse of the midportion of the nose (Fig. 7.2). Its presence usually indicates defects in the septum, which in turn are most likely due to septal perforation (causes described above) or prior septal surgery. Saddle nose can complicate the dissection and transposition of a septal flap in the same way as septal perforation and septal scarring. Twisted nose deformity can be due to deformity of septum, nasal bones, and nasal tip cartilage and soft tissue (Fig. 7.3). Such significant external signs often predict significant internal derangements which may necessitate extra-nasal surgery at the same setting to augment the approach while facilitating optimal correction of the patient's anatomy.

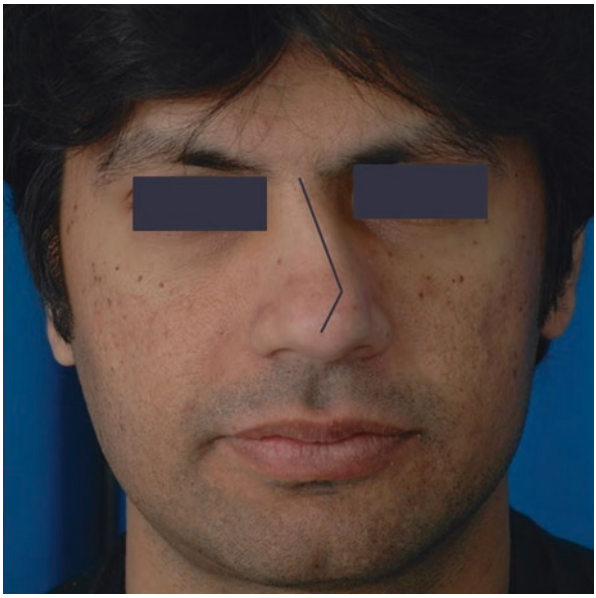

Fig. 7.3 Twisted nose. Line drawn to more easily identify the deviation of the nose and underlying septum. Correction of the septum will likely require osteotomies and may be better suited as a staged procedure

A sleep history should also be obtained prior to surgery. Sleep apnea is extremely common in acromegaly, with obstructive sleep apnea occurring in 60–70% of patients and central sleep apnea occurring in about 20–30% of patients [12, 13]. Obstructive sleep apnea is also very common in patients with Cushing's disease, occurring in about one-half of patients [14]. Acromegaly and Cushing's disease are among the most common indications for transsphenoidal surgery. Because untreated sleep apnea increases operative risk, it is important to determine if a patient suffers from this disease, and if so, patients should be guided into proper preoperative intervention [15, 16].

Imaging

Preoperative imaging protocols should optimally be modified to include the nasal septum and paranasal sinuses. This can often be achieved with MRI alone and the authors find that a T2-weighted series is helpful in understanding the paranasal sinus anatomy when a bone-windowed CT scan is not available. While not a substitute for direct visualization of the septum, one retrospective evaluation of axial acquired MRI images was able to predict the need for septoplasty (unpublished data from UVA). In that series, we were able to demonstrate a 56% probability of requiring a septoplasty if the maximal septal deflection was greater than 3 mm from ideal. This increased to 93% when the deflection was greater than 5 mm. Despite this, most otolaryngologists are accustomed to visualizing nasal anatomy with coronally oriented series. As such, collaboration between neurosurgical and otolaryngologic colleagues will be necessary to define the optimal sequences that will facilitate the

collection of all pertinent anatomical information. We have found that when CT angiography is performed to define the intracranial vascular anatomy, these images can completely obviate the need of any additional CT imaging of the sinuses. The narrow slice thickness typically required for these studies is a superb adjunct for visualizing bony structures and pinpointing sinus and septal anomalies. The results of the imaging can determine the role of intraoperative stereotactic image guidance.

Postoperative Rhinologic Evaluation

The rhinologic evaluation of the postoperative patient is tailored to the patient's procedure and any preexisting conditions that may have been corrected or potentially exacerbated during surgery. An informal review of practice patterns at a recent international educational conference indicated wide variability in the frequency of scheduled follow-up visits. At our institution, we prefer to see patients between 2 and 4 weeks after surgery if any adjunctive procedures were performed and from 4 to 8 weeks postoperatively for any straightforward sellar approaches without local flap reconstructions. At each of these visits, the potential complications of endonasal skull base surgery are surveyed including issues with epistaxis, cerebrospinal fluid (CSF) leak, and worsened or iatrogenically induced sinusitis.

Intraoperative bleeding is a common complication of transsphenoidal surgery. The endoscopic approach often necessitates blind introduction of instruments into the surgical field, which can increase the risk of intranasal trauma and mucosal bleeding. The turbinates and septum are at particularly high risk for trauma. Subsequent scab formation may facilitate the development of postoperative synechia or adhesions between the septum and turbinates. These synechiae can impair nasal functions such as airflow and olfaction and are ideally identified and managed early in the postoperative course before they become more fibrotic. The timing of follow-ups may need to be adjusted based on the type of surgery performed and the likelihood of synechia formation to optimize prophylactic care.

Postoperative bleeding is most likely to originate in nasal structures, and the management strategy generally depends on the location and briskness of the bleeding. More severe postoperative bleeding often arises after iatrogenic injury to the posterior nasal branch of the sphenopalatine artery. This bleeding can be managed through electrocautery or chemical cautery with endoscopic assistance followed by repacking of the nares. Nasal mucosal bleeding is common but generally less brisk than arterial bleeding. Packing the nares with Afrin-soaked pledgets for several minutes is usually sufficient to terminate the bleeding. Electrocautery can be effective if packing does not successfully terminate bleeding.

CSF leak is a significant concern in transsphenoidal surgery. Classically, it arises along the surgical site in the posterior wall of the sphenoid sinus, but it is also a concern from a rhinologic perspective given the fragility of the basal lamella attachment of the middle turbinate and the thin walls of the ethmoid roof and cribriform plate. Middle turbinectomy can generally be avoided in endonasal transsphenoidal

surgery without compromising surgical view. When performed, however, this portion of the operation can be a common cause of CSF leak [17]. Minimizing surgical manipulation of the middle turbinate can prevent many CSF leaks from the anterior skull base. CSF leaks discovered postoperatively manifest as rhinorrhea and can be a life-threatening concern. Evaluation requires detailed endoscopic visualization of the ethmoid and sphenoid skull base for signs of clear rhinorrhea. This can be accomplished with the patient in forward head tilt position to optimize localization. Additionally, collecting any fluid and analyzing it for the presence of beta-2 (tau) transferrin can differentiate CSF from any retained saline from nasal irrigations. Ideally, evaluation of any postoperative rhinorrhea should be limited to those cases with continued drainage for 24–48 h after cessation of nasal saline applications.

Septal perforations arise from disruptions in the septal mucosa and can occur in the setting of tears in the septal flaps postoperatively. Small hematomas can go on to form septal perforations, especially in areas where underlying bone or cartilage has been resected. Medical management is the first line of therapy and normally consists of nasal saline sprays and other nasal moisturizers. This helps minimize symptoms but does not resolve the perforation. Surgical correction centers on the use of mucosal, mucoperichondrial, and mucoperiosteal flaps.

Postoperative sinusitis is a common rhinologic complication of transsphenoidal surgery and has been found in the sphenoid sinus of 6.2–7.5% of patients who underwent transsphenoidal hypophysectomy [18, 19]. Roughly half of these cases resolved with medical management. The remainder required endoscopic sphenoidotomy [18, 19]. In other cases, a mucocele forms in the sphenoid sinus, requiring either marsupialization of the sinus or complete resection [20]. Rarely, a superimposed infection can give rise to a pyocele [21]. This complication is rare and is surgically managed in similar fashion to sphenoid mucocele. Given the high frequency of isolated sphenoid sinusitis and/or mucocele in postoperative transnasal transsphenoidal surgery patients, a low index of suspicion and high readiness to initiate medical therapy for sinusitis is justified. Other intranasal infections can also arise after surgery, although this is rare.

Nasal crusting is a very common complaint in the postoperative period. Most cases resolve after a few months of supportive treatment with nasal sprays. Although more disruption of nasal anatomy is associated with greater crusting, the use of nasoseptal flaps does not change the severity or duration of nasal crusting [22]. In addition to nasal saline sprays or irrigations, emollients and aqueous-based gels can also be used to minimize the symptomaticity of this finding.

Generally, rhinologic complications of endoscopic transnasal transsphenoidal surgery are mild, self-limited, and subordinate to neurosurgical concerns. That said, sinonasal quality of life has been shown to temporarily decrease after transsphenoidal endoscopic surgery in a measurable fashion [23]. The decrease in sinonasal quality of life reaches a nadir approximately two weeks after surgery, but with appropriate pre- and postsurgical rhinologic evaluation and treatment, long-term sinonasal quality of life may exceed the patient's presurgical baseline [24].

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Imaging of the Sella and Parasellar Region

8

Amar P. Patel, Vivek P. Patel, and Max Wintermark

Introduction

The complex and intricate anatomy of the sella turcica and parasellar region of the skull base serves as a host to a diverse variety of pathologies. Imaging is paramount in diagnosing these pathologies and preventing transshpenoidal surgery complications by accurately and precisely characterizing sella and parasellar pathologies prior to surgery. This chapter will focus on the preoperative imaging of frequently encountered sella and parasellar pathologies.

Imaging Anatomy of the Pituitary and Parasellar Region

The sella turcica or "Turkish saddle" is a midline depression in the sphenoid bone that houses the pituitary gland and is bound anteriorly by the tuberculum sellae and posteriorly by the dorsum sellae.

The pituitary gland consists of two functional and morphological parts: the anterior pituitary or adenohypophysis and the posterior pituitary or neurohypophysis. The adenohypophysis is further divided into three parts: the pars tuberalis, pars intermedia, and pars distalis. Suprasellar adenomas may arise from the pars tuberalis [13]. After "total" hypophysectomy, the pars tuberalis may house residual

A.P. Patel, MD • M. Wintermark, MD, MBA (✉)
Department of Radiology, Neuroradiology Division,
Stanford University School of Medicine, Stanford, CA
e-mail: max.wintermark@gmail.com

V.P. Patel, MD, PhD
Department of Radiology, Stanford University School of Medicine, Stanford, CA

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_8

functioning pituitary tissue [10]. The pars intermedia may contain tiny cysts that are thought to be embryologic remnants of Rathke's cleft [10]. The pars distalis secretes prolactin, growth hormone, thyroid stimulating hormone, follicular stimulating hormone, luteinizing hormone, adrenocorticotrophin, and melanocyte stimulating hormone. The neurohypophysis is also divided into three parts: the posterior lobe of the pituitary, infundibular stem, and the median eminence of the hypothalamus. Vasopressin and oxytocin are synthesized in the hypothalamus, transported through the infundibular stem, and stored in the posterior pituitary, where they are released in the blood stream.

The size of the pituitary gland changes with age. Normal maximum pituitary height measures 6 mm in infants and children, 8 mm in men and postmenopausal women, 10 mm in women of child-bearing age, and 12 mm in pregnant and postpartum women [10]. The pituitary infundibulum is wider at its origin from the hypothalamus and smoothly tapers inferiorly to its insertion into the pituitary gland. Normal maximum pituitary stalk thickness measures 3.5 mm at the median eminence, 2.8 mm at its midpoint, 2.0 mm at its most inferior aspect, and 2.5 mm overall in children [14].

The adult adenohypophysis is isointense to brain parenchyma on all magnetic resonance imaging (MRI) sequences while the neurohypophysis is intrinsically T1 hyperintense (Fig. 8.1). Both the adenohypophysis and the neurohypophysis can be T1 hyperintense at birth. However, the adenohypophysis T1 hyperintensity decreases by six weeks of age [8]. Patients with central diabetes insipidus often lose the distinct T1 hyperintensity of the neurohypophysis.

The sella turcica is bound laterally by the paired cavernous sinuses. From cranial to caudal, cranial nerves (CN) III, IV, V1, and V2 are found within the lateral wall of the cavernous sinus which is made of a thick double layer of dura mater. Inferomedially within the cavernous sinuses are the cavernous segments of the internal carotid arteries (ICAs) surrounded by sympathetic nerve fibers. CN VI is inferolateral to the ICA.

Imaging Protocol

MRI is the imaging modality of choice for evaluation of sellar and parasellar pathologies due to superb soft-tissue contrast and high spatial resolution. Multidetector computed tomography (CT) is used for evaluation of calcification, central skull base osseous anatomy, and in patients with contraindications to MRI. MRI is superior to CT in determining pathology, location, establishing extent of regional disease, and characterizing lesions as solid, cystic, hemorrhagic, or fatty.

An appropriate MRI sella protocol is necessary in pre- and postoperative assessment of sella and parasellar pathologies at 1.5 T and 3.0 T. Protocols should utilize proper field of view and slice thickness in obtaining multiplanar axial, coronal, and sagittal images, including T1-, T2-, and diffusion-weighted sequences before and after the administration of intravenous gadolinium contrast. Three-millimeter-thin coronal and sagittal T1-weighted postcontrast images are obtained to best detect

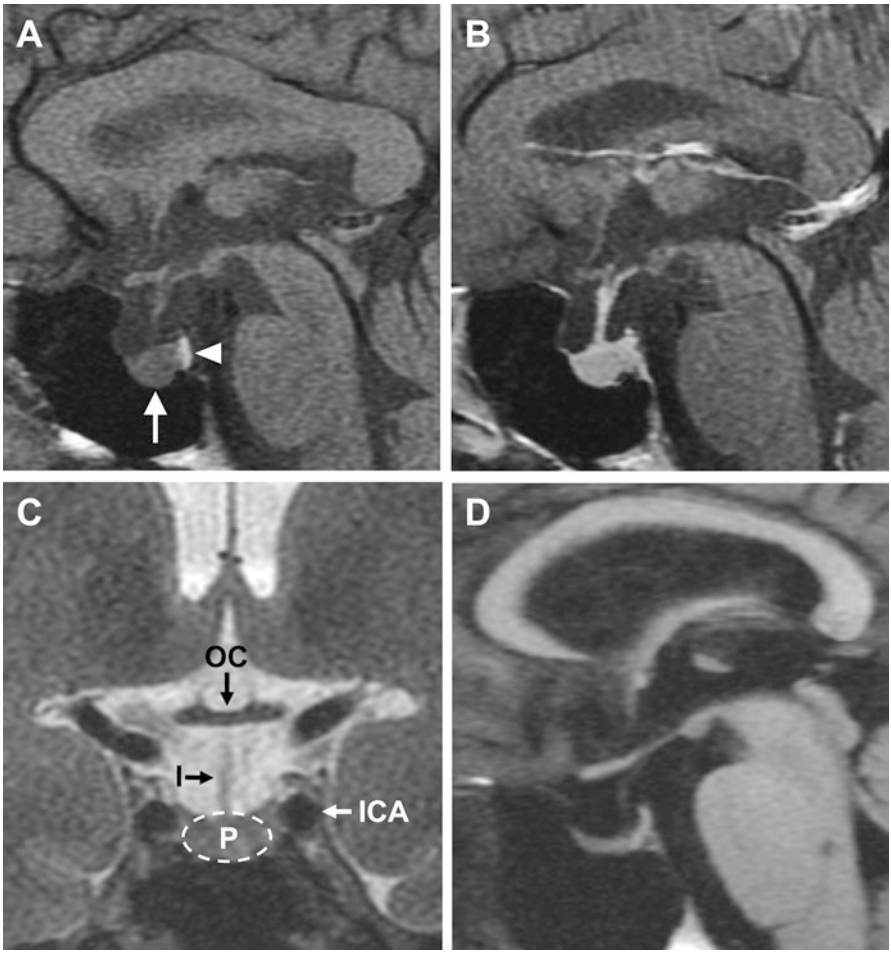

Fig. 8.1 Normal appearance of the pituitary gland on MRI. (**a**) Sagittal T1-W image shows the isointense adenohypophysis (*arrow*) and the hyperintense neurohypophysis (*arrowhead*). (**b**) Sagittal T1-W contrast-enhanced image. (**c**) T2-W fast spin echo (FSE) image shows the normal anatomy in the coronal plane with nearby structures: *I* infundibulum, *P* pituitary gland, *OC* optic chiasm, and *ICA* internal carotid artery. (**d**) T1-W FLAIR sequence image shows a partially empty sella

microadenomas. Dynamic contrast-enhanced MRI improves pituitary gland microlesion detection over standard postcontrast sequences [2]. At our institution, dynamic imaging involves the rapid acquisition of a set of coronal T1-weighted images through the sella for about 20 s after the administration of a bolus of intravenous contrast at 4 mL/s. Three-millimeter-thin section of heavily T2-weighted volumetric sequences are obtained to improve characterization of cystic lesions within the pituitary gland and visualization of the cranial nerves. Table 8.1 details the MRI sella protocol used at our institution.

Table 8.1 MRI sella protocol on 3.0 T

Series description	Pulse sequence	FOV	Slice thickness	Slice spacing	Scan range
AX DWI	Spin Echo	24	5	0	Whole brain
AX T2 FSE	Fast Spin Echo	24	5	0	Whole brain
COR T2 THIN	Fast Spin Echo	18	3	0.3	Centered on sella
COR T1 THIN	Spin Echo	18	2	0.5	Centered on sella
SAG T1 THIN	Spin Echo	18	2	0.5	Centered on sella
Contrast	Inject at 4 mL/s				
COR T1 FSE DYNAMIC +C	Fast Spin Echo	16	2.5	0.5	5 Slices centered on sella
COR T1 THIN +C	Spin Echo	18	2	0.5	Centered on sella
SAG T1 THIN +C	Spin Echo	18	2	0.5	Centered on sella
AX T1 SE WB +C	Spin Echo	24	5	0	Whole brain

Coil: HD 8Ch High Res Brain Array by Invivo
Optional: SAG/COR GRE for Pituitary Apoplexy

Pathology of Sella and Parasellar Region

Tumors

Pituitary Adenoma

Pituitary adenoma is the most common intrasellar mass. A microadenoma measures less than 10 mm while a macroadenoma measures 10 mm or more in greatest maximum dimension. Pituitary adenoma is a benign, slow-growing tumor that frequently arises within the sella and occasionally from the pituitary stalk in the suprasellar cistern. Ectopic adenomas can rarely be found in the sphenoid sinus, nasopharynx, cavernous sinuses, and sphenoid bone. Adenomas may be functional or nonfunctional. Functional adenomas are named after the hormone they produce. Prolactin-secreting adenomas or prolactinomas are the most common functional pituitary microadenomas and are typically associated with prolactin levels greater than 150 ng/mL [18]. Prolactinomas may present with amenorrhea, galactorrhea, and infertility in women or gynecomastia, loss of libido, and impotence in men. Adrenocorticotropic-secreting adenomas cause hypercortisolism and Cushing's disease while TSH-secreting adenomas cause hyperthyroidism and thyrotoxicosis. Growth-hormone-secreting adenomas cause gigantism in children and acromegaly in adults.

On precontrast T1-weighted imaging, microadenomas are usually hypointense or isointense to normal pituitary gland; however, intratumoral hemorrhage may cause intrinsic T1 hyperintensity. Microadenomas appear more variable on T2-weighted imaging. Most pituitary adenomas are readily resectable at surgery and softer adenomas have high T2 signal. Other tumors are more adherent to surrounding tissues and firmer adenomas have low T2 signal [14]. After the administration of intravenous gadolinium contrast, most microadenomas are hypoenhancing

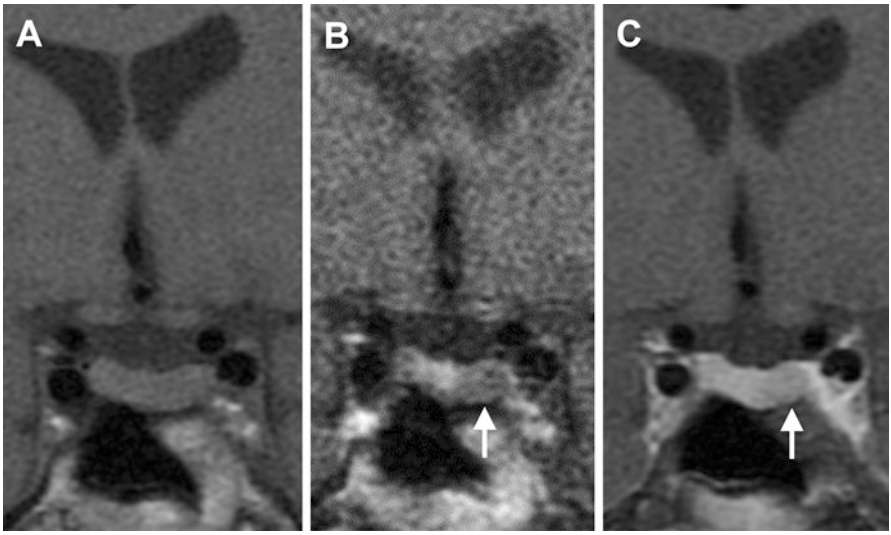

Fig. 8.2 Microadenoma. (**a**) T1-W image demonstrates a subtle contour abnormality in the left half of the gland. (**b**) Early dynamic postcontrast sequences show a hypointense adenoma (*arrow*) due to delayed enhancement. (**c**) Appearance of the adenoma on delayed contrast-enhanced images can vary, with hypoenhancement being most common (*arrow*)

relative to normal pituitary gland. On dynamic contrast-enhanced MRI, a microadenoma and pituitary gland differentially uptake contrast where the microadenoma usually enhances more slowly and less intensely than the pituitary gland (Fig. 8.2). While most microadenomas tend to enhance relatively less than the normal pituitary gland on postcontrast imaging, some tumors avidly retain contrast on delayed imaging and appear hyperenhancing relative to the normal pituitary gland which washes out contrast earlier.

Patients with microadenomas receive medical therapy or transsphenoidal microsurgical resection depending on the clinical scenario. Medical therapy with bromocriptine or other dopamine agonists such as cabergoline lowers prolactin secretion to normal in 80% of patients. Surgery may be performed based on the clinical presentation and laboratory results even if a microadenoma is not seen on MRI [6]. The overall sensitivity for the detection of adenomas with MRI is greater than 90%. Transsphenoidal surgery is curative in 60–90% of cases. Radiation therapy and radiosurgery are helpful for patients unable to undergo surgery and/or incompletely resected or recurrent tumors.

Macroadenomas measure greater than 10 mm and often cause smooth expansion of the sella turcica and bony remodeling due to their slow growth. Macroadenomas can be locally aggressive and invade the cavernous sinuses, sphenoid sinus, suprasellar cistern, or dorsum sella. Due to internal hemorrhage, cystic changes, and/or necrosis, macroadenomas often have a wide range of signal intensities on MRI. Enhancement is also variable with most tumors moderately to avidly enhancing after contrast (Fig. 8.3). When patients are preoperatively treated with bromocriptine,

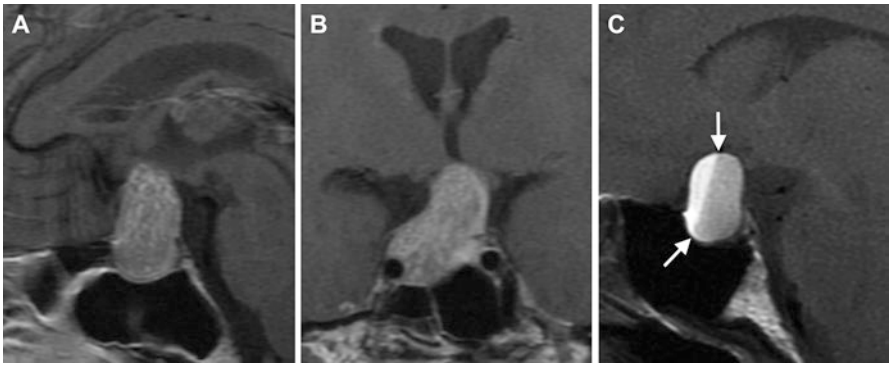

Fig. 8.3 Macroadenoma. (**a**, **b**) Sagittal (**a**) and coronal (**b**) T1-W contrast-enhanced images show a large macroadenoma. The adenoma also has mass effect on the surrounding structures, including the optic chiasm (the patient reported bitemporal hemianopsia). Macroadenomas typically do not compress the vessels they encase. (**c**) Sagittal noncontrast T1-W image shows a hyperintense mass with a fluid-fluid level (*arrows*), which suggests recent hemorrhage into an adenoma (pituitary apoplexy)

macroadenomas often develop small areas of hemorrhage [7]. Precontrast T1 hyperintensity may indicate the presence of hemorrhage.

Preoperative identification of the normal pituitary gland, often compressed away by a large macroadenoma, is important in preventing pituitary insufficiency and preserving pituitary tissue at surgery. Complete tumor resection at surgery is limited by cavernous sinus invasion. Twenty-one percent of macroadenomas had invaded the cavernous sinus at the time of surgery [15]. The most specific sign of cavernous sinus invasion on MRI is when the adenoma encases the cavernous ICA. Parasellar meningiomas in the cavernous sinus rather than macroadenomas are more likely to narrow the lumen of the cavernous ICA. Imaging findings that make cavernous sinus invasion less likely include normal pituitary gland interposed between the adenoma and the cavernous sinus, intact medial venous compartment, and 25% or less encasement of the cavernous ICA [21]. Cavernous sinus invasion affects whether the tumor is likely to be completely resected versus debulked with surveillance imaging or coexistent radiotherapy. Macroadenoma recurrence rates are approximately 15% at 8 years and 35% at 20 years.

Pituitary Apoplexy

Pituitary apoplexy is an acute clinical syndrome with headache, nausea, visual deficits, ophthalmoplegia, altered mental status, and endocrine deficiencies most commonly caused by hemorrhage or infarction within a preexisting pituitary macroadenoma. MRI signal intensity of pituitary apoplexy depends on the subtype of apoplexy (hemorrhagic or ischemic) and the time of imaging compared to the time of symptom onset (i.e., hemoglobin state of oxygenation). A fluid-fluid level is often seen with hemorrhagic pituitary apoplexy (Fig. 8.3c). At our institution, sagittal and coronal gradient echo sequences are obtained to better demonstrate "blooming" from blood products in cases of hemorrhagic pituitary apoplexy. Diffusion-weighted MRI may demonstrate high signal in acute pituitary adenoma infarction [19].

Adenomas that have undergone infarction commonly demonstrate peripheral rim enhancement. Sphenoid sinus mucosal thickening is a frequent finding with pituitary apoplexy. Treatment for pituitary apoplexy includes surgical decompression or possible medical management.

Craniopharyngioma

Craniopharyngioma is a slow-growing benign tumor derived from Rathke's pouch epithelium. Craniopharyngiomas have a bimodal distribution by age with peak incidence in children 5–14 years old and older adults 65–74 years old [4]. Tumors are divided into two histological subtypes: adamantinomatous and papillary.

Adamantinomatous tumors occur in children and young adults and are mostly mixed solid and cystic heterogeneously enhancing suprasellar/sellar tumors. In 80% of cases high T1 signal is seen within one or more cysts on MRI because of proteinaceous contents. In 90% of cases, calcification is seen along the periphery of individual cystic components on CT (Fig. 8.4). Adamantinomatous tumors are

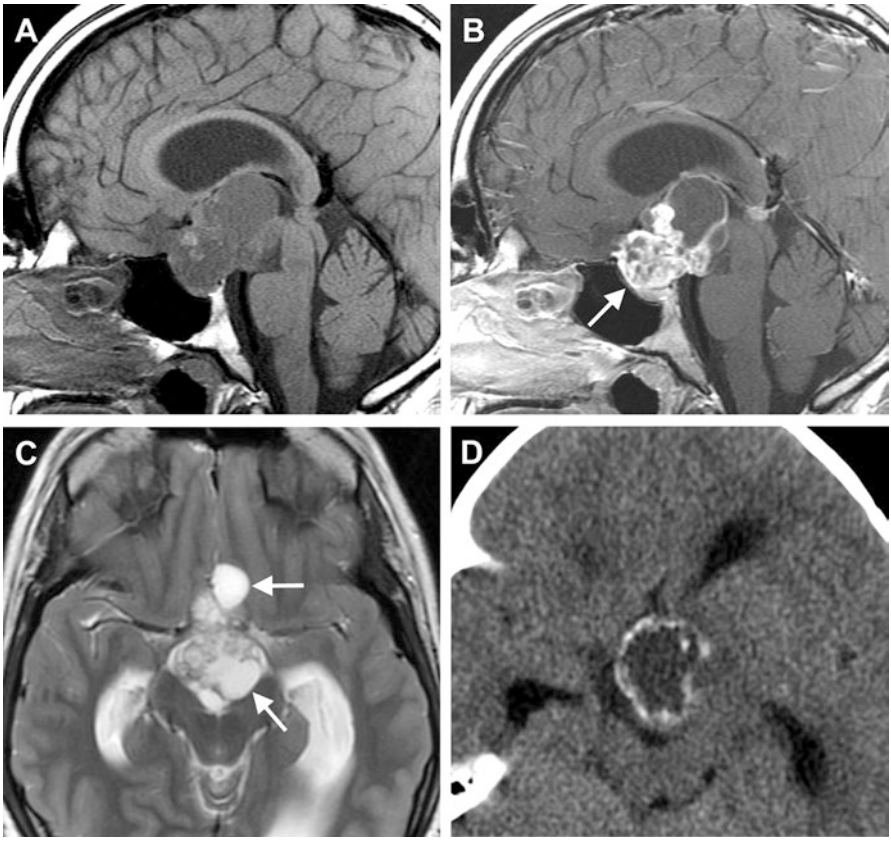

Fig. 8.4 Craniopharyngioma, adamantinomatous type. (**a**–**c**) T1-W image shows a large heterogenous suprasellar mass (**a**) in a 20-year-old patient with strong enhancement of the solid component on postcontrast images (**b** *arrow*). (**c**) Axial T2-W sequence shows hyperintense cystic components, as indicated by the arrows. (**d**) CT scan characteristically shows peripheral rim calcifications, as shown in another pediatric patient

aggressive and tend to invade surrounding structures, thereby often preventing gross total surgical resection. Adjuvant radiotherapy is often administered with incomplete resection or recurrent disease.

Papillary craniopharyngiomas usually occur in adults as a predominantly solid, noncalcified, and homogenously enhancing suprasellar tumor [20]. Gross total resection of papillary craniopharyngioma is usually curative. Craniopharyngioma size influences prognosis with a 20% recurrence rate for tumors measuring less than 5 cm and an 83% recurrence rate for tumors measuring greater than 5 cm.

Tuber Cinereum Hamartoma

Tuber cinereum hamartoma or hypothalamic hamartoma is a congenital nonneoplastic lesion consisting of heterotopic gray matter. It is typically located between the mammillary bodies and infundibulum and can be sessile or pedunculated. Sessile tuber cinereum hamartomas result in gelastic seizures while pedunculated tuber cinereum hamartomas result in precocious puberty [3]. Hypothalamic hamartomas are isointense to gray matter on both T1- and T2-weighted images and do not enhance after contrast administration (Fig. 8.5).

Meningioma

Meningiomas account for up to 18% of all intracranial tumors and are the second most common sellar/parasellar tumors after pituitary adenomas [16]. A meningioma can arise from the dura mater overlying the planum sphenoidale, tuberculum sellae, diaphragma sellae, lesser and greater sphenoid wings, cavernous sinus, or optic nerve sheaths. Most commonly occurring in the fourth to seventh decade of life, meningiomas are generally isointense relative to cortical gray matter on T1- and T2-weighted images. Contrast administration demonstrates intense homogenous enhancement of the extra-axial tumor due to its highly vascular nature. A broad dural attachment or "dural tail" can be observed in up to 57% of cases [16] (Fig. 8.6).

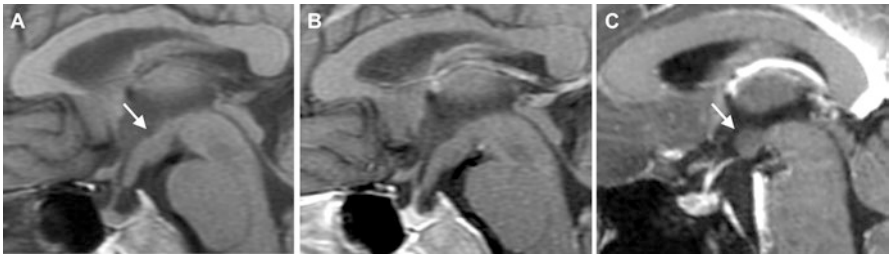

Fig. 8.5 Tuber cinereum hamartoma (or hypothalamic hamartoma). (**a**) T1-W image shows a mass (*arrow*) that is isointense to the gray matter. It does not have any enhancement after contrast administration (**b**) This is an example of the sessile type. Incidental note is made of absent pituitary bright spot. (**c**) Another example of a hypothalamic hamartoma (*arrow*) with no enhancement after contrast

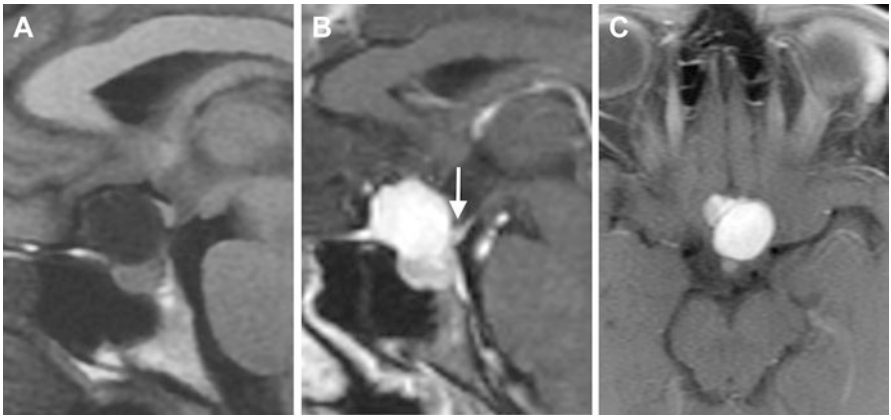

Fig. 8.6 Meningioma. (**a**) T1-W image shows a large hypointense mass. (**b**) Sagittal high-resolution 3D T1-W isotropic image shows a hyperintense mass. A dural tail can be seen (*arrow*). (**c**) Axial postcontrast image shows homogenous enhancement of the mass

Associated CT findings include bony hyperostosis and tumor calcification which occurs in approximately 20% of cases.

Parasellar meningiomas commonly invade the cavernous sinus. When meningiomas invade the cavernous sinus, they have a tendency to encase the cavernous segment of the ICA and are more likely than macroadenomas to narrow the ICA lumen. Meningiomas also cause a higher frequency of CN palsies when cavernous sinus invasion is present [18]. If asymptomatic and small, a meningioma may be followed with serial imaging. Treatment options include surgery and/or radiation therapy. Preoperative angiography and embolization may be used to reduce intraoperative blood loss. When surgical resection is incomplete, radiotherapy or radiosurgery may be used as adjunctive treatment. Peritumoral brain edema, best detected on T2-weighted images, is associated with higher rates of surgical complication and tumor recurrence.

Meningiomas confined to the cavernous sinus may mimic trigeminal nerve schwannomas. Dynamic contrast-enhanced MRI can be helpful in distinguishing between meningioma and schwannoma. Meningiomas generally show early contrast enhancement whereas schwannomas typically show slower gradual contrast enhancement [12].

Schwannoma

Schwannomas account for up to 8% of all primary intracranial tumors and are the most common tumors observed in the region of the cavernous sinus. Parasellar schwannomas may arise from CNs III, IV, V1, V2, or VI. However, CN V is the most commonly involved cranial nerve. On MRI, schwannomas appear as well-defined tubular or lobulated T2-hyperintense and homogenously enhancing tumors. Rarely, these tumors can have foci of cystic change or intratumoral hemorrhage.

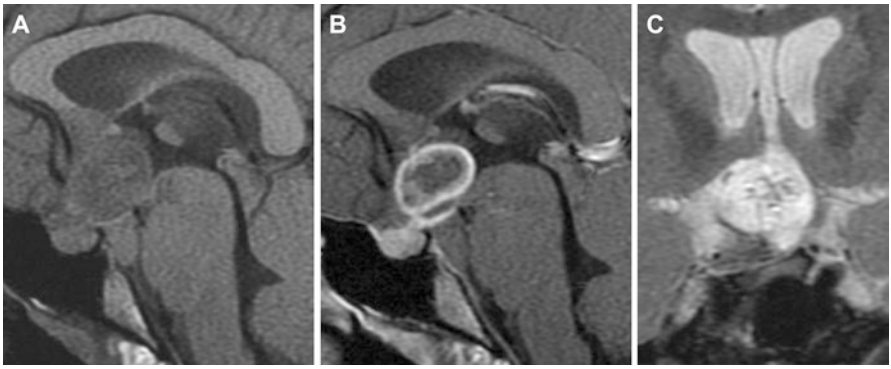

Fig. 8.7 Pilocytic astrocytoma. (**a**) T1-W image shows a hypointense mass. (**b**) Postcontrast T1-W image shows heterogenous enhancement of the mass. (**c**) The mass is T2 hyperintense

Hypothalamic Pilocytic Astrocytoma

Astrocytoma is the most common pediatric central nervous system tumor. A hypothalamic astrocytoma is typically a low-grade tumor and most commonly a pilocytic astrocytoma. Hypothalamic-pituitary dysfunction including diabetes insipidus may be due to a pilocytic astrocytoma in the hypothalamus [17]. Most cases of diencephalic syndrome, characterized by failure to thrive and emaciation despite normal caloric intake, are due to a hypothalamic pilocytic astrocytoma [17]. On MRI, the tumor is mixed solid and cystic, T2-hyperintense, and enhances after contrast administration (Fig. 8.7). Resection, stereotactic radiosurgery, radiation therapy, and chemotherapy are potential treatments for hypothalamic pilocytic astrocytomas.

Germ Cell Tumors

Germinoma is the most common intracranial germ cell tumor. Germinomas occur most frequently in the pineal region; however, approximately 25–35% occur in the suprasellar cistern. Patients with hypothalamic germinomas may present with diabetes insipidus in the second to third decade of life. Supportive imaging findings of a suprasellar germinoma include a solid, avidly and homogenously enhancing hypothalamic/infundibular tumor simultaneously presenting with a pineal mass (Fig. 8.8). Germinomas may demonstrate restricted diffusion on DWI because of high tumor cellularity. Germinomas spread through CSF seeding, so MRI of the entire craniospinal axis is important prior to surgery to evaluate for leptomeningeal metastasis. Measurement of serum and cerebrospinal fluid (CSF) β-human chorionic gonadotropin and α-fetoprotein may assist in the diagnosis of germinoma [14].

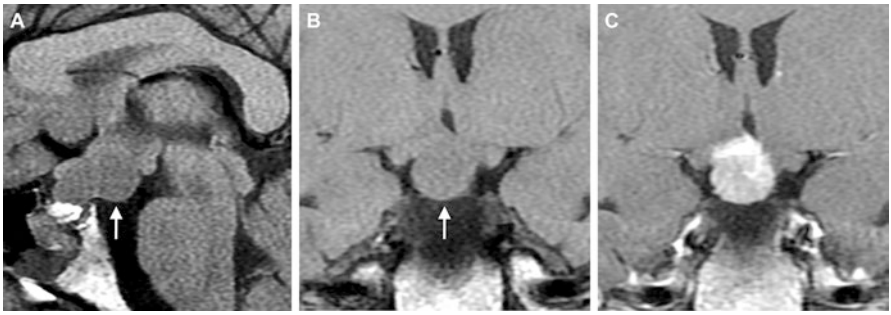

Fig. 8.8 Germinoma. (**a**, **b**) T1-W image shows an isointense mass centered in the pituitary stalk (*arrows*). (**c**) The mass has strong homogenous enhancement after contrast

Chordoma

Chordoma is a locally aggressive tumor arising from primitive notochord remnants. In the skull base, it most often originates in the midline from the spheno-occipital synchondrosis, but less commonly it may arise unilaterally from the petrous apex. Chordoma may have sellar and/or parasellar locations, and they rarely arise in the nasopharynx, maxilla, paranasal sinuses, or intradural region [11]. CT is useful for identifying tumoral calcification and determining the extent of bony destruction. MRI is the imaging modality of choice for both pre- and posttreatment evaluation. Chordomas typically replace the high-T1-signal-intensity fat of the clivus with low- to intermediate-T1-signal-intensity tumor. Chordomas characteristically demonstrate very high T2-signal intensity, a finding that likely reflects the high fluid content of vacuolated cellular components [11]. Chordomas avidly enhance with contrast administration (Fig. 8.9d-f). Optimum treatment algorithm includes radical surgical resection with adjuvant radiosurgery or radiotherapy. Tumor extent and surgeon's preference determine surgical strategies and patients may undergo multiple surgeries to maximize tumor resection.

Chondrosarcoma

While chordomas typically arise in the midline, chondrosarcomas typically arise just off the midline. Chondrosarcoma is a malignant cartilaginous bone tumor which may originate from the clivus and involve the sella turcica and has a tendency to be centered at the petro-occipital fissure. Rings and arcs of calcification, typical of chondroid tumors like chondrosarcoma, may be seen on CT. On MRI, the tumor appears markedly hyperintense on T2-weighted images and demonstrates variable enhancement (Fig. 8.9a-c).

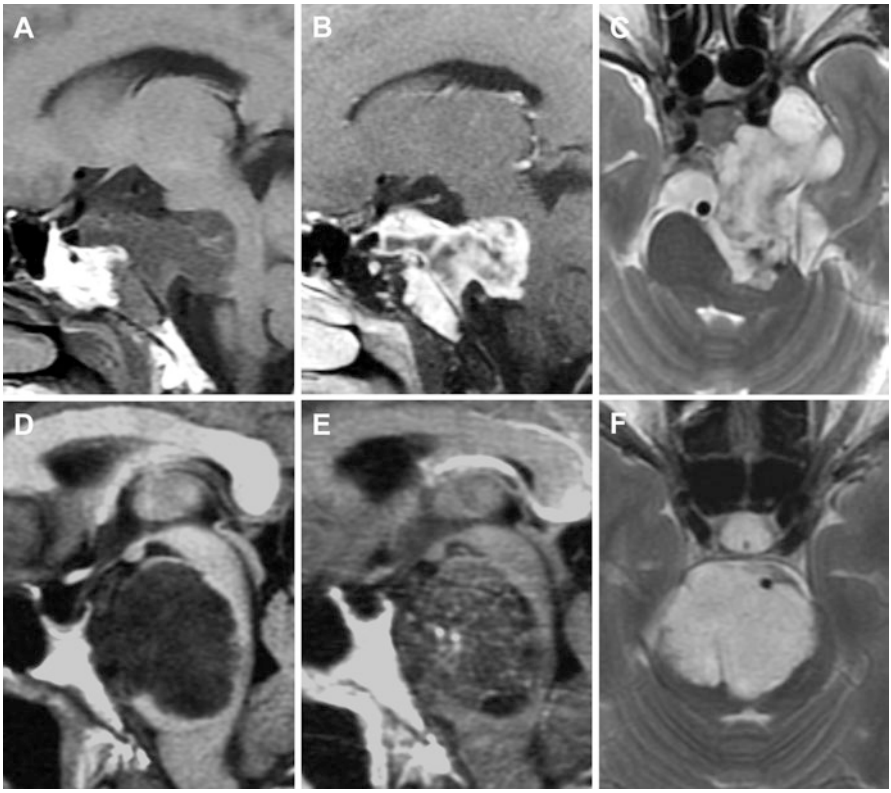

Fig. 8.9 Chondrosarcoma (**a**–**c**) and chordoma (**d**–**f**). (**a**–**c**) T1-W images show a hypointense mass (**a**) that has a hetergenous enhancement after contrast administration (**b**). The mass is T2-hyperintense (**c**). Chondrosarcomas are typically paramedian and centered on the petro-occipital fissure. (**d**–**f**) T1-W FLAIR sequences show a hypointense mass (**d**) that has a heterogenous and honeycomb-like enhancement after contrast due to low T1-signal areas within the tumor (**e**). The mass is also T2-hyperintense (**f**). Chordomas are typically centered on the clivus

Tumor-like Lesions

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH) is a neoplastic disease with clonal proliferation of Langerhans cells. Bone lesions are the most common radiologic manifestation of LCH and occur in approximately 80% of patients [22]. The skull is the most common flat bone involved, followed by the mandible, ribs, pelvis, and spine. The most common clinical manifestation of LCH involving the central nervous system is diabetes insipidus. The normal posterior pituitary "bright spot" is absent on T1-weighted MRI. Approximately 70% of patients will also show thickening and enhancement of the pituitary infundibulum [22] (Fig. 8.10).

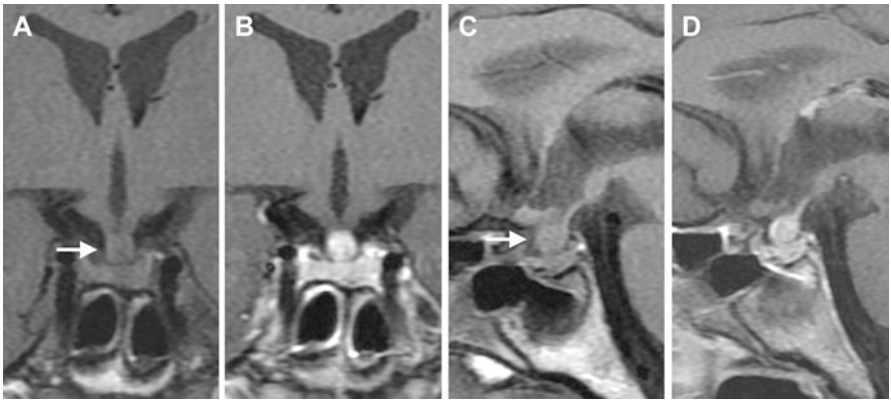

Fig. 8.10 Langerhans cell histiocytosis. (**a**, **c**) Coronal and sagittal T1-W images show a suprasellar mass in the region of the pituitary stalk (*arrow*). (**b**, **d**) The lesion enhances on postcontrast images

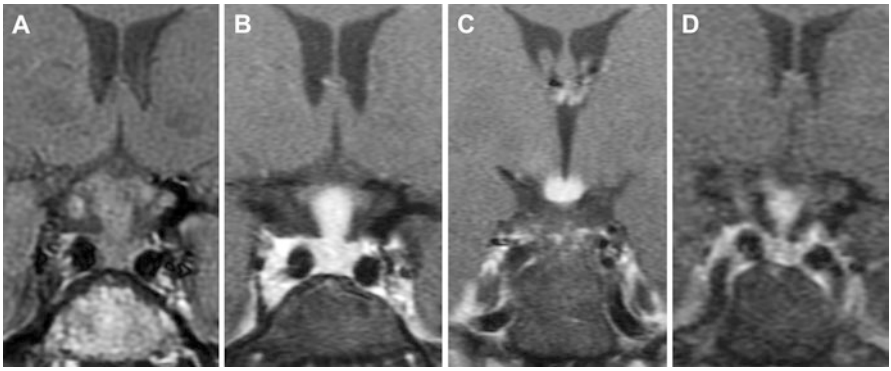

Fig. 8.11 Neurosarcoid. (**a**, **b**) T1-W image shows an isointense thickening of the pituitary stalk (**a**) that has strong homogenous enhancement after contrast (**b**). (**c**) The hypothalamus is often also involved and again shows homogenous enhancement. (**d**) Postcontrast image after the patient was treated with steroids shows a decrease in the degree of thickening and enhancement of the pituitary stalk

Sarcoidosis

Sarcoidosis is a multisystem inflammatory disease characterized by noncaseating granulomas. Sarcoidosis involving the central nervous system may have a wide spectrum of imaging findings, including thickening of the hypothalamus and pituitary infundibulum. Abnormal cranial nerve, leptomeningeal, and perivascular parenchymal enhancement may also be seen. Resolution of imaging findings following treatment with corticosteroids and/or immunosuppressive therapy typically lags after resolution of clinical symptoms (Fig. 8.11).

Cysts

Rathke's Cleft Cyst

A Rathke's cleft cyst is a congenital benign nonneoplastic sellar and/or suprasellar cyst arising from the pars intermedia located between the adenohypophysis and the neurohypophysis. Most cysts are asymptomatic and incidentally found at imaging; however, some may be symptomatic. The cyst signal intensity on MRI is variable depending on the contents (e.g., protein, cholesterol, hemorrhage). Predominately serous cysts are T1-hypointense and T2-hyperintense, whereas predominantly mucinous cysts are T1-hyperintense and T2-hypointense. A T1-hyperintense and T2-hypointense nonenhancing intracystic nodule is seen in 77% of cases and is diagnostic for a Rathke's cleft cyst [5] (Fig. 8.12). Asymptomatic patients may undergo surveillance imaging. Symptomatic patients may undergo surgical drainage, partial excision, or complete resection. Postoperative surveillance imaging is important because up to 18% of Rathke's cleft cysts can recur.

Epidermoid Cyst

Epidermoid cyst is a congenital ectodermal inclusion cyst which may occur in the suprasellar cistern or parasellar region. The cyst insinuates cisterns and encases neurovascular structures and cranial nerves. Epidermoid cysts are isointense to hyperintense relative to CSF on T2-weighted imaging, do not completely suppress signal on FLAIR, and are characteristically hyperintense on diffusion-weighted imaging (Fig. 8.13e-h). Total surgical resection is desirable; however, subtotal excision may be performed if there is risk of damaging the cranial nerves or injuring the vessels. Recurrence is common if epidermoid cysts are incompletely removed. Rarely subarachnoid dissemination of contents may occur during surgery or in the postoperative course, leading to chemical meningitis.

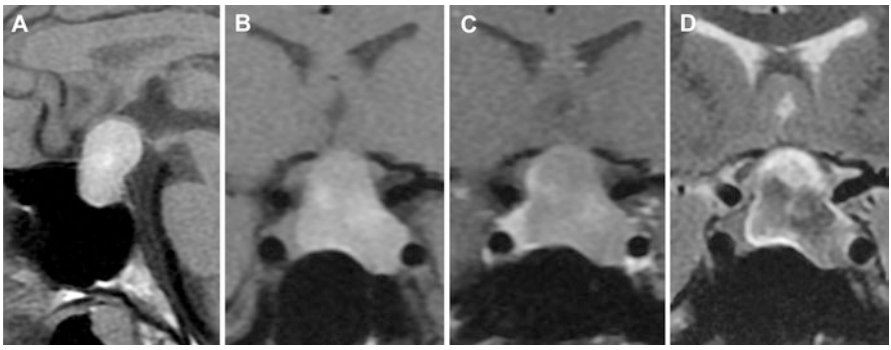

Fig. 8.12 Rathke's cleft cyst. (**a**, **b**) T1-W image shows a well-defined midline cyst. It can appear hyperintense due to the high protein content. (**c**) No enhancement of the cyst is seen after contrast administration. (**d**) T2-W image shows a hypointense intracystic nodule, which is a typical feature of this lesion

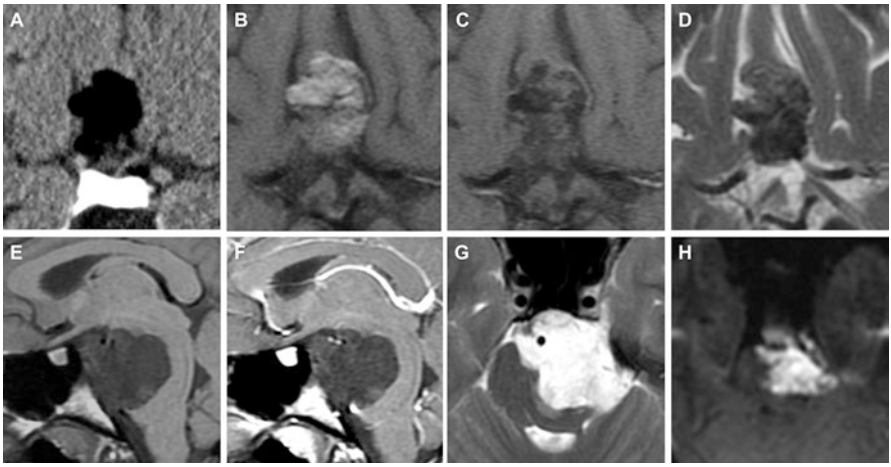

Fig. 8.13 Dermoid (**a**–**d**) and epidermoid cysts (**e**–**h**). (**a**–**d**) CT scan shows a mass with fat attenuation (**a**). Axial T1-W images show heterogenous hyperintensity (**b**) that suppresses with fat saturation (**c**). Dermoid cysts often have a variable signal on T2-W sequences (**d**). (**e**–**h**) T1-W images show a hypointense mass (**e**) that does not enhance after contrast (**f**). Epidermoid cysts, which can be in- or off-midline, are T2-hyperintense (**g**) and restrict on DWI (**h**)

Dermoid Cyst

Dermoid cysts are also congenital inclusion cysts but less common than epidermoid cysts. A dermoid cyst is almost always found in the midline and may present with cyst rupture into the subarachnoid space causing aseptic chemical meningitis. Due to lipid content, dermoid cysts are predominately hyperintense on T1-weighted imaging (Fig. 8.13a-d). T1-hyperintense fat signal within the subarachnoid space or ventricles is pathognomonic for a ruptured dermoid cyst.

Miscellaneous Nontumoral Conditions

Intracranial Hypotension

Imaging findings of nontumoral conditions such as intracranial hypotension may include enlargement of the pituitary gland. Failure to recognize this potential pitfall may cause one to mistake the imaging findings for a pituitary adenoma or hyperplasia. Some additional supportive imaging findings of intracranial hypotension include "sagging" midbrain, subdural effusions, diffuse pachymeningeal thickening and enhancement, and enlarged epidural veins [1] (Fig. 8.14).

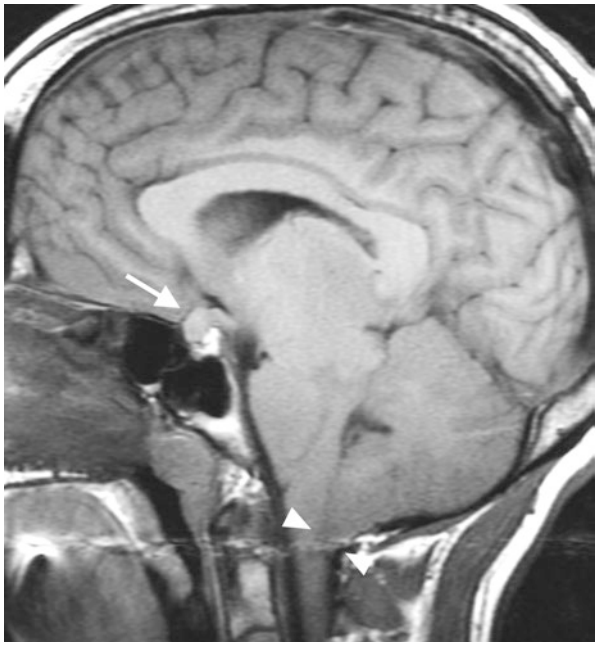

Fig. 8.14 Intracranial hypotension. Sagittal T1-W image shows prominence of the pituitary with a convex superior margin (*arrow*), which is a common feature of intracranial hypotension. Other supporting features include a peg-like deformity (*arrowheads*) of the cerebellar tonsils (downward displacement of the cerebellar tonsils), crowding of the foramen magnum and posterior fossa, and sagging of the midbrain

Empty Sella

An empty sella is usually an incidental finding of no clinical significance. An incomplete or absent diaphragma sella permits herniation of the arachnoid with CSF inferiorly into the sella turcica, flattening the pituitary gland against the sella floor (Fig. 8.1d). This finding may be a normal variant. It can also be seen in the setting of elevated intracranial pressure, such as in pseudotumor cerebri, and in the setting of pituitary atrophy.

Operative Planning

Preoperative imaging may be obtained for pathology characterization or stereotactic localization. The extent of disease (e.g., cavernous sinus invasion, central skull base foramina involvement) may alter the surgical approach, so a diagnostic sella protocol MRI is usually necessary prior to surgery. Knowledge of potentially clinically significant anatomic variants such as medially located ICAs within the sella turcica or sphenoid bone dehiscence around the ICAs is essential in avoiding complications such as arterial injury during transsphenoidal surgery.

Postoperative Imaging Evaluation

It is important to obtain a baseline contrast-enhanced MRI after surgical resection to evaluate for residual tumor and/or complications. On follow-up imaging, comparison with baseline postoperative imaging is helpful in differentiating between residual tumor and fibrosis/scar. Residual tumor will often have the same signal intensity and enhancement as the preoperative tumor. Progressive interval lesion growth on serial imaging studies is specific for tumor.

Postoperative hemorrhage, hemostatic agents, and packing material alone or in combination cause heterogeneous signal on postoperative MRI. Autologous fat grafts are routinely used to prevent or treat CSF leaks and are intrinsically T1-hyperintense and suppress signal on fat-saturated postcontrast imaging. Gelfoam (The Upjohn Company, Kalamazoo, Ml) is a common surgical packing material that is variable in appearance but most often with a T1-hypointense irregular center and a larger T2-hypointense area [9]. Methylmethacrylate can also be used as packing material in the sella and is hypointense on all sequences.

Conclusion

The sella and parasellar regions are anatomically and pathologically complex areas. Familiarity with the essential preoperative imaging findings of various sella and parasellar pathologies allows complete assessment of disease extent. Comprehensive disease characterization with sella protocol MRI allows for superior preoperative planning and therefore helps surgeons avoid transsphenoidal surgery complications.

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Classification, Pathobiology, Molecular Markers, and Intraoperative Pathology

9

M. Beatriz S. Lopes

Pituitary Neuroendocrine Tumors

Introduction

The majority of pituitary neuroendocrine tumors are pituitary adenomas; pituitary carcinomas are a rare condition, accounting for only 0.1–0.2% of all pituitary neuroendocrine tumors [2]. Adenomas are benign tumors confined to the sella turcica; however, invasive adenomas are frequent [3]. Adenomas may sometimes occur in he sphenoid sinus when they are designated as "ectopic" pituitary adenomas [4].

Pituitary adenomas predominantly affect females between the third and sixth decades. However, no age group is spared [1]. Adenomas are uncommon in the pediatric population, and most tumors of childhood are clinically functioning adenomas [5]. Incidental adenomas can be found in nearly 14% of autopsied patients [6].

Molecular Genetics of Pituitary Adenomas

The mechanisms involved in human pituitary adenoma tumorigenesis and tumor progression are still not completely understood. Pituitary adenomas appear to develop through a multistep and multi-causal process in which endocrine factors, hereditary genetic disposition, and specific somatic mutations may serve as contributory factors.

M. Beatriz S. Lopes, MD, PhD (✉)
Department of Pathology, University of Virginia School of Medicine and Health System, Charlottesville, VA, USA
e-mail: MSL2E@hscmail.mcc.virginia.edu

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_9

Table 9.1 Most common tumors of the pituitary and sellar region

Neuroendocrine tumors
Pituitary adenoma
Pituitary carcinoma
Non-neuroendocrine tumors
Pituicytoma
Granular cell tumor
Spindle cell oncocytoma
Gangliocytoma
Tumors of nonpituitary origin
Craniopharyngioma
Germinoma and other germ cell tumors
Langerhans cell histiocytosis
Meningioma
Chordoma

Pituitary adenomas arise mostly in a sporadic manner and only a minority of adenomas is part of hereditary or familial syndromes [7]. Hereditary conditions associated with development of pituitary adenomas include the multiple endocrine neoplasia (MEN) syndromes MEN1 and MEN4 [8, 9], the Carney's complex [10–12], the McCune-Albright syndrome [11, 12], the hereditary pheochromocytoma/paraganglioma syndrome (related to succinate dehydrogenase [SDH] genes) [13, 14], the familial isolated pituitary adenoma (FIPA) syndrome [15], and the X-linked acrogigantism (XLAG) associated with GPR101 microduplication [16]. Most of the tumors associated to these familial syndromes secrete GH and/or PRL and rarely are nonfunctioning adenomas. A rare primitive, embryonal-like pituitary tumor, the pituitary blastoma, is part of the DICER1 syndrome [17, 18].

The primary genetic defect in the great majority of sporadic adenomas remains unknown. A number of oncogenes and tumor suppressor genes have been recognized as potential participants in tumorigenesis of pituitary adenomas. The most commonly found genetic alteration in sporadic tumors is somatic mutations in the *GNAS* gene found in 40% of sporadic somatotroph adenomas resulting in upregulation of the cAMP pathway [19, 20]. The *GNAS* gene mutation is rarely identified in other pituitary adenoma subtypes occurring in only 10% of clinically nonfunctioning pituitary adenomas and in 5% of corticotroph adenomas [20].

Nonsyndromic gigantism has been related to inactivating germ-line mutations on the aryl hydrocarbon receptor-interacting protein (*AIP*) gene [21] and more recently due to germ-line or somatic duplication of the *GPR101* gene similar to the familial X-linked acrogigantism (XLAG) [22].

Mutations in the *USP8* (encoding ubiquitin-specific protease 8) gene, leading to an upregulated EGFR pathway, have been identified in about 36–62% of sporadic corticotroph adenomas [23–25].

Other oncogenes and tumor suppressor genes that have been occasionally reported in pituitary adenomas include the oncogene *PTTG* (pituitary tumor-transforming gene),

the proto-oncogene *H-ras*, and the tumor suppressor genes *RB* and *TP53* [26, 27]. However, it seems that these genes are not directly associated with pituitary adenoma tumorigenesis but may play a role during progression and malignant transformation of these tumors [28, 29].

Classification of Pituitary Adenomas

Pituitary adenomas are clinically classified into two main groups: the *clinically functioning adenomas* and the *clinically nonfunctioning adenomas*, according to whether or not an endocrine syndrome is present. Most adenomas are functioning tumors and include prolactin (PRL)-producing, growth hormone (GH)-producing, adrenocorticotropic hormone (ACTH)-producing, and thyrotropin-stimulating hormone (TSH)-producing adenomas [6]. About a third of pituitary adenomas are unassociated with either clinical or biochemical evidence of hormone excess [30]. This group includes the gonadotroph adenomas that produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and the null cell adenomas. These clinically nonfunctioning adenomas commonly present with symptoms related to local mass effect such as headaches, neurologic deficits in the cranial nerves including visual field disturbances, and mild hyperprolactinemia due to pituitary stalk compression (the so-called stalk effect). In addition, adenomas may be designated as "silent adenomas" when the patients do not show any clinical signs or hormonal elevation in the serum but the tumor demonstrates hormone production by immunohistochemistry.

Pituitary adenomas are histopathologically classified by the World Health Organization (WHO) classification according to the hormone content of the tumor cells as assessed by immunohistochemical stains [31] (Table 9.2). This immunohistochemical classification provides significant information for clinical practice. Moreover, the WHO classification recognizes the role of transcription factors (mainly Pit-1, SF-1, Tpit.) in tumor's differentiation according to cellular lineage(s), in the regulation of specific pituitary hormones, and possible pathogenesis of these tumors. Recognizing this new data, the current WHO classification has adopted the pituitary-cell lineage for designation of the adenomas [31].

Several cell-restricted transcription factors have been recognized during pituitary cytodifferentiation [32]. The acidophilic cell lineage, including somatotrophs, lactotrophs, and thyrotrophs, require Prop1 and Pit-1 for their differentiation [33, 34]. In gonadotrophs, steroidogenic factor-1 (SF-1) and GATA-2 play positive roles in activation of gonadotroph-specific genes determination and differentiation [35–37]. The transcription factors NeuroD1 and Tpit have been identified as restricted to pro-opiomelanocortin (POMC)-expressing lineages corticotrophs and melanotrophs [38, 39].

These transcription factors have been localized in human pituitary tumors in a pattern similar to normal pituitary cell differentiation and, therefore, may serve as diagnostic tools. Somatotroph, lactotroph, and mixed somato-lactotroph adenomas have been demonstrated to express strong nuclear staining for Pit-1 while

Table 9.2 Pathological classification of pituitary adenomas

Adenoma types	Morphological variants	Pituitary hormones by immunohistochemistry	Transcription factors
Somatotroph adenoma	Densely granulated adenoma	GH ± PRL, α-subunit	Pit-1
	Sparsely granulated adenoma	GH ± PRL	Pit-1
	Mammosomatotroph adenoma	GH + PRL (in same cell) ± α-subunit	Pit-1
	Mixed somatotroph-lactotroph adenoma	GH + PRL (in different cells) ± α-subunit	Pit-1
Lactotroph adenoma	Sparsely granulated adenoma	PRL	Pit-1
	Densely granulated adenoma	PRL	Pit-1
	Acidophilic stem cell adenoma	PRL, GH (focal and variable)	
Thyrotroph adenoma		β-TSH, α-subunit	Pit-1
Corticotroph adenoma	Densely granulated adenoma	ACTH	Tpit
	Sparsely granulated adenoma	ACTH	Tpit
	Crooke's cell adenoma	ACTH	Tpit
Gonadotroph adenoma		β-FSH, β-LH, α-subunit (various combinations)	SF-1, GATA2
Null cell adenoma		None	None
Plurihormonal adenomas	Pit-1-positive plurihormonal adenoma (previously termed Silent subtype 3 adenoma)	GH, PRL, β-TSH ± α-subunit	Pit-1
	Adenomas with unusual immunohistochemical combinations	Various combinations	

corticotroph and gonadotroph adenomas are negative for Pit-1 expression [40–42]. Tpit is specific to POMC-producing adenomas including corticotroph adenomas [43, 44]. SF-1 expression is characteristic of gonadotroph adenomas [45], and it is a differentiating marker between gonadotroph and null cell adenomas [46]. Pertinent to diagnostic surgical practice, Pit-1 and SF-1 have been clinically validated with reliable monoclonal antibodies for their utilization in the majority of clinical laboratories; thus far, dependable commercial sources for Tpit antibodies are not available [31].

Specific Subtypes of Pituitary Adenomas

Lactotroph Adenomas

Clinical Features Lactotroph adenomas (Fig. 9.1) (prolactinomas, PRL-secreting adenomas) correspond to nearly 80% of functioning pituitary tumors and about 40–50% of all pituitary adenomas [6, 47]. However, most of the patients with prolactinomas are treated clinically with dopamine agonist therapy. Therefore, the frequency of prolactinomas in surgical series tends to be smaller [47].

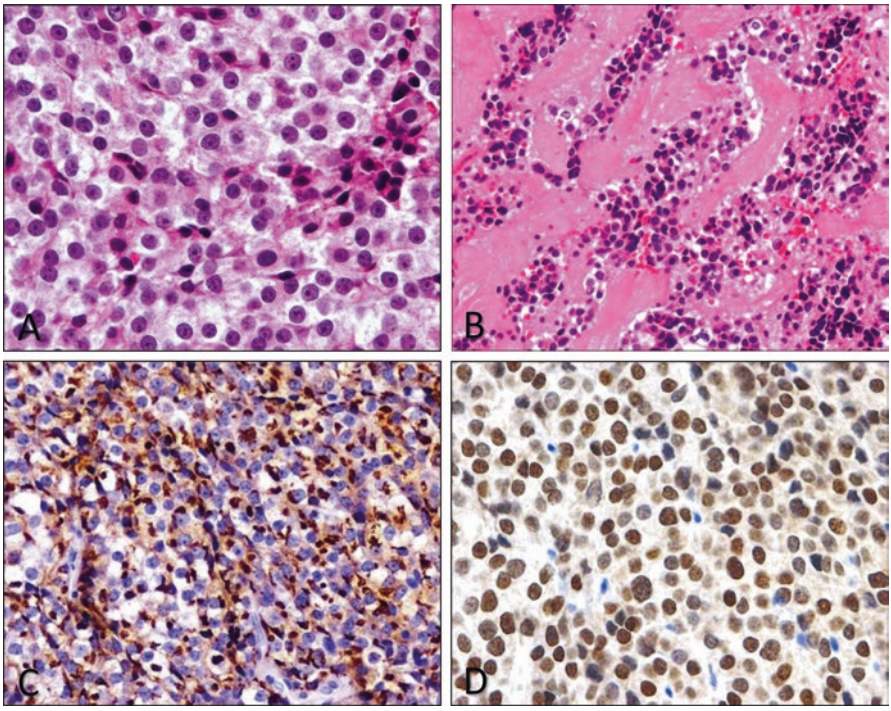

Fig. 9.1 Lactotroph adenomas. (**a**) Lactotroph adenomas are mostly chromophobic tumors with central hyperchromatic nucleus. (**b**) Tumors that have been medically treated prior surgery show smaller cells and prominent perivascular fibrosis. (**c**) PRL immunoreactivity is typically seen in a paranuclear location in lactotroph adenomas. (**d**) Lactotroph adenomas strongly express the Pit-1 transcription factor (**a**, **b** H&E; **c** PRL IHC; **d** Pit-1 IHC)

In women, the majority of lactotroph adenomas is a microadenoma and occurs during reproductive age presenting with oligoamenorrhea, galactorrhea, and infertility [47]. Conversely, in men and elderly women, tumors are usually macroadenomas and are most commonly associated with symptoms of tumoral mass including headaches, neurologic defects, and visual loss [47]. Impotence and decreased libido are also common symptoms of hyperprolactinemia in males [47].

The great majority of lactotroph adenomas are sporadic tumors; however, lactotroph adenomas may be associated with familial syndromes, most commonly MEN1 syndrome [8, 48]. In that setting, lactotroph adenomas may present as multiple adenomas or double adenomas with other type of variant such as corticotroph or somatotroph adenoma [48].

Histopathology Lactotroph adenomas are composed of medium-sized cells with chromophobic or slightly acidophilic cytoplasm and a central, oval nucleus. Small nucleoli can be present. Approximately 10–20% of cases show microcalcifications. The tumors may also produce an amyloid-like substance, forming small hyaline bodies [49].

Lactotroph adenomas can be divided into densely and sparsely granulated variants, although the clinical significance of this distinction is questionable [49, 50]. Sparsely granulated adenomas are the most common tumors and their cells resemble actively secreting lactotrophs of the normal pituitary gland. Immunohistochemistry shows reactivity for PRL in a pattern of staining very characteristic with localization near the nucleus in a "dot-like" pattern or also known as "Golgi" pattern [49]. In addition, lactotroph adenomas are immunoreactive for the acidophilic lineage Pit-1 transcription factor.

As commented above, the majority of patients with lactotroph adenomas are treated to some degree with dopamine agonists. These drugs have direct effect on the tumor cells inducing atrophy of lactotrophs with resultant tumor shrinkage [47]. Histologically, tumors from patients previously treated with such drugs are composed of smaller tumor cells with shrinkage of the cytoplasm and hyperchromasia of the nuclei in addition to various degrees of perivascular and interstitial tumoral fibrosis [51, 52].

Acidophilic Stem Cell Adenoma A special variant of lactotroph adenomas is the acidophilic stem cell adenoma that represents only the minority of PRL-producing tumors. Although initially regarded as a mixed GH-PRL-secreting adenoma (see below), most of the patients present with symptoms of hyperprolactinemia [53]; acromegaly is uncommon, and GH levels are often normal. The majority of the tumors are rapidly growing macroadenomas with invasive features. Because most of the patients have clinical features of hyperprolactinemia, the diagnosis is of clinical importance in that these tumors may be mistaken for the more benign prolactinomas.

By light microscopy, acidophilic stem cell adenomas are chromophobic with focal oncocytic changes of the cytoplasm. Immunoreactivity for PRL and, to a lesser extent, GH is present in the cytoplasm of the same tumor cells. Oncocytic change is characteristic with the presence of large amounts of mitochondria that can be highlighted by immunostaining with mitochondrial markers or ultrastructural analysis when available [53].

Somatotroph Adenomas

Clinical Features Somatotroph adenomas (Fig. 9.2) (somatotrophinomas, GH-secreting adenomas) correspond to about 20% of pituitary adenomas. Patients present with signs and symptoms of acromegaly and/or gigantism and high serum GH and insulin-like growth factor I (IGF-I) levels. Acromegaly affects both sexes with similar incidence, and the mean age at diagnosis is 40–45 years [54]. Symptoms of acromegaly are usually slowly progressive with an average delay until diagnosis of approximately 10 years [54]. Less commonly, adenomas arise in children and adolescents before the epiphyseal closure of the long bones resulting in gigantism. Around 20% of childhood gigantism and 8–11% of acromegaly in young individuals have been associated with the *AIP* gene and at least half of those have a positive family history resulting in FIPA [12, 15, 21]. Early-onset pediatric gigantism (<5 years at diagnosis) has been linked to the X-linked acrogigantism (XLAG) syndrome [22].

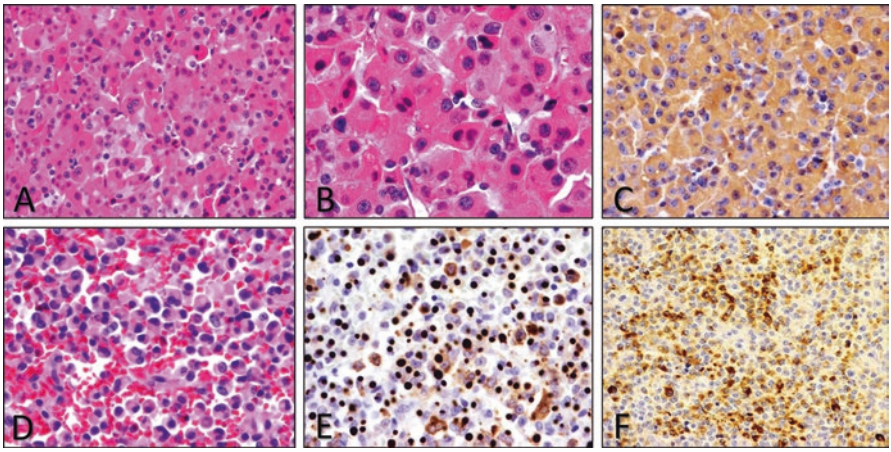

Fig. 9.2 Somatotroph adenomas. In somatotroph adenomas, the evaluation of histopathological and immunohistochemical features is essential in the recognition of the two major subtypes of adenomas, the densely granulated and the sparsely granulated GH-cell adenomas. Due to the different clinical and biological behaviors of these two subtypes, their recognition is essential for patient management. (**a**, **b**) Densely granulated somatotroph adenomas show large cells with eosinophilic granular cytoplasm and central nucleus with prominent nucleoli. (**c**) The tumor shows intense and diffuse immunostain for GH. (**d**) Sparsely granulated somatotroph adenomas have a chromophobic cytoplasmic appearance showing a paranuclear eosinophilic inclusion named "fibrous bodies" that are highlighted by cytokeratin immunostaining (**e**). (**f**) In sparsely granulated adenomas, the GH immunoreactivity is typically more focal within the cell and less prominent than densely granulated adenomas (**a**, **b**, **d** H&E; **c**, **f** GH immunohistochemistry (IHC); **e** CAM 5.2 IHC)

Most acromegalic patients have macroadenomas when first diagnosed, many of them with suprasellar expansion and parasellar invasion [55]. Consequently, symptoms secondary to an expanding tumor mass, including headaches and visual field defects, are commonly present. In about 30–50% of the patients, co-secretion of PRL with GH by the tumor results in signs and symptoms of hyperprolactinemia [54, 55]. Mixed GH/PRL-secreting tumors are discussed below.

Histopathology Somatotroph adenomas are either eosinophilic or chromophobic by H&E staining. These histological attributes reflect the amount of secretory granules present in the cell cytoplasm and characterize the two subtypes of somatotroph adenomas – the *densely granulated* and the *sparsely granulated* somatotroph adenomas. The densely granulated adenomas are characterized by eosinophilic tumor cells with the cytoplasm showing considerable granularity and reflecting great numbers of secretory granules seen at the ultrastructural level. The nucleus tends to be central and oval with prominent nucleoli. The sparsely granulated somatotroph adenomas are composed by smaller tumor cells with chromophobic cytoplasm and an eccentric nucleus. In the cytoplasm, paranuclear eosinophilic structures called "fibrous bodies" are seen [50, 56]. These structures represent accumulations of intermediate filaments and tubular formations at the ultrastructural level and are strongly immunoreactive for cytokeratin [56].

The two subtypes of somatotroph adenomas, densely and sparsely granulated adenomas, can be distinguished by both immunohistochemistry and ultrastructural analysis [50]. Immunohistochemical stains show a variable degree of GH immunoreactivity in the two subtypes of adenomas. In the densely granulated adenomas, GH immunostain diffusely occupies the entire cytoplasm of the tumor cells and tends to be dispersed diffusely within the entire tumor. By contrast, in the sparsely granulated adenomas, GH immunostain is focal within the tumor and tends to be localized in a paranuclear distribution, similar to the Golgi pattern seen in prolactinomas [50]. As discussed above, the most characteristic feature of the sparsely granulated adenomas is the presence of "fibrous bodies," that can be easily identified by low-molecular weight cytokeratin immunostaining [56].

The distinction of the two subtypes of GH-cell adenomas is of importance since these tumors appear to have different clinical behavior. The sparsely granulated GH adenomas exhibit more aggressive biologic behavior than the densely granulated tumors [55, 57, 58]. In addition, the response of tumors to adjuvant medical treatment also differs according to the subtype of somatotroph adenoma [59].

All variants of somatotroph adenomas are immunoreactive for the transcription factor Pit-1 that drives acidophilic lineage of differentiation [40, 41]. A number of somatotroph adenomas show secondary reactivity for other pituitary hormones [55, 60] including focal PRL immunostain, even in patients without clinical or biochemical evidence of hyperprolactinemia. Similarly, the presence of immunoreactivity for the glycoprotein hormones β-FSH, β-LH, α-SU, and less frequently β-TSH, can be demonstrated in a number of GH-secreting adenomas [55].

Adenomas Secreting GH and PRL

As mentioned above, a large percentage of GH-secreting adenomas also secrete PRL. About half of the patients with somatotroph adenomas in our institution presented signs and symptoms of both acromegaly and hyperprolactinemia [55]. In this group of adenomas, two morphologic tumor types can be identified: the *mixed GH-cell and PRL-cell adenoma* and the *mammosomatotroph cell adenoma* [55, 60]. As described in the lactotroph section, the acidophilic stem cell adenoma may also present with slight signs of acromegaly [55, 60]. These mixed secreting tumors constitute about 8% of pituitary adenomas [2]. Their recognition is significant since it has clinical and prognostic implications since they behave more aggressively than any pure somatotroph adenomas with a lower surgical cure rate [2, 55, 61].

Mixed GH-Cell and PRL-Cell Adenoma The predominant clinical feature of mixed GH-cell and PRL-cell adenomas is acromegaly. Signs and symptoms of hyperprolactinemia are not always apparent. Morphologically, the tumors are similar to somatotroph adenomas with an eosinophilic/chromophobic appearance. Immunostains are demonstrated for both GH and PRL with varying degrees of staining and distribution. The two cell types may form small groups or may be scattered. At the ultrastructural level, these adenomas are bimorphous tumors, consisting of two separate cell populations, densely or sparsely granulated GH cells and PRL cells [61].

Mammosomatotroph Cell Adenoma This rare GH/PRL-producing tumor accounts for less than 2% of all pituitary adenomas and about 8% of tumors associated with acromegaly [2, 62]. Similar to mixed GH-cell and PRL-cell adenomas, these tumors are associated with elevated circulating GH levels and acromegaly; hyperprolactinemia is less common. Histologically, these adenomas are acidophilic on H&E stain and immunohistochemistry demonstrates the presence of GH and PRL in the cytoplasm of the same tumor cells. These findings have been confirmed by double-labeling studies as well as by immunoelectron microscopy [62]. Ultrastructural analysis demonstrates a well-differentiated adenoma composed of a monomorphous cell population which contains features of GH and PRL cells [62]. The tumor cells are mostly similar to densely granulated GH cells, but with irregular secretory granules of variable sizes (200–2000 nm) and contain granule extrusions and extracellular deposits of secretory material, a feature consistent with PRL-cell differentiation [62].

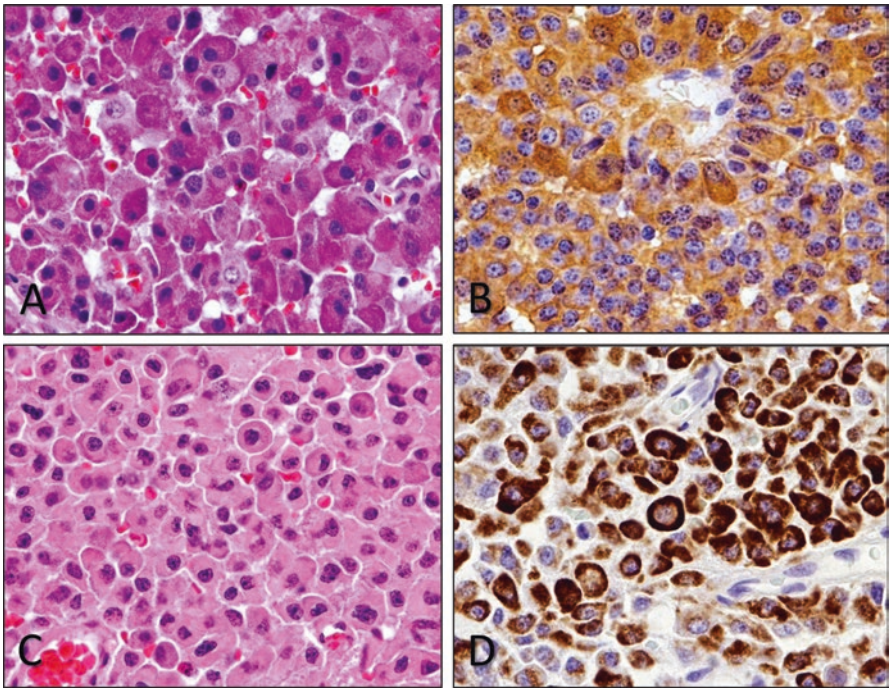

Fig. 9.3 Corticotroph adenomas. (**a**) The majority of the adenomas are basophilic and densely granulated, with large central nucleus and prominent nucleolus. (**b**) Immunostaining for ACTH shows strong and diffuse immunoreaction in these densely granulated adenomas. (**c**, **d**) Crooke's adenomas are composed of large numbers of cells displaying hyaline bands within the cytoplasm that are composed by cytokeratin (**d**). Crooke's cell adenomas are believed to clinically behave more aggressively than otherwise conventional corticotroph macroadenomas (**a**, **c** H&E; **b** ACTH IHC; **d** CAM 5.2 IHC)

Corticotroph Adenoma

Clinical Features Corticotroph adenomas (Fig. 9.3) (corticotrophinomas, ACTH-secreting adenomas) associated with Cushing's disease represent approximately 10–15% of all adenomas [63]. Cushing's disease is more frequent in females (3.5:1 female-to-male ratio) [64], and affects patients within a varying age, with a peak between ages of 30 and 40 years. In children, Cushing's disease is rare and tends to have more aggressive clinical course and lower cure rate than adults [65, 66]. Different than adults, Cushing's disease arising in prepubertal children is more common in males than females [67].

The great majority of ACTH-secreting adenomas are microadenomas and approximately 15% are invasive at the time of surgery [3].

The majority of corticotroph adenomas are sporadic. They occur infrequently in an inherited setting including FIPA associated with *AIP* gene mutations, MEN4 and MEN1 [68, 69]. Rare cases of sporadic tumors have shown germ-line mutations in genes associated with familial pituitary adenomas including *AIP* gene [11] and MEN1gene [11]. As commented above, somatic mutations in the *USP8* gene are present in about 40–60% of sporadic corticotroph adenomas [23–25].

Histopathology Corticotroph adenomas are usually basophilic by H&E stain. The cells have very distinct cytoplasmic borders and tend to touch each other in a "tile-like" arrangement. Papillary formations are very common. The majority of the tumors are densely granulated, i.e., with abundance of secretory granules that are strongly and diffusely immunoreactive for ACTH and strong positive by PAS. In contrast, a minority of adenomas are sparsely granulated and composed of faint basophilic or chromophobic cells showing weak or patchy positivity for ACTH. Corticotroph adenomas express the transcription factor Tpit [43, 44]; however, at the moment reliable antibodies for clinical usage are not available. In addition, other peptides related to the pro-opiomelanocortin (POMC) precursor molecule, including β-lipotropin, β-endorphin, and α-melanocyte-stimulating hormone, may also be expressed by tumor cells with no clinical significance [70].

Crooke's Cell Adenoma Occasionally, tumors have large numbers of Crooke's cells and are designated Crooke's adenomas. Crooke's cells correspond to corticotroph cells with accumulation of cytokeratin intermediate filaments that appear on H&E staining as hyaline bundles encircling the cytoplasm, giving a "target-cell" appearance. By immunohistochemistry, the cells have a ring-like cytokeratin expression and ACTH immunoreaction dislocated to the cell periphery and juxtanuclear region. Crooke's changes commonly present in the normal pituitary gland of Cushing's patients and in patients with other pathologic or iatrogenic hypercortisolemic state and are believed to be a direct action of high serum levels of cortisol on the pituitary cells [71].

Crooke's adenomas most commonly are macroadenomas and more prevalent in females [72]. The majority of adenomas are clinically functioning with Cushing's disease symptoms, but about a third of the cases may present as non-functioning tumors [72]. By histopathology, the tumors are comprised of more than 50% of the cells with Crooke's changes [73]. Crooke's adenomas may have

a clinically more aggressive behavior than the average corticotroph macroadenoma [72, 73].

Silent Corticotroph Adenoma These variants of corticotroph adenomas are characterized by immunoreactivity for ACTH in the absence of either clinical signs of Cushing's disease or serum levels reflecting excess ACTH secretion by the patients. The majority of these tumors are macroadenomas and patients present with signs and symptoms of a mass lesion [74, 75]. Characteristically, silent corticotroph adenomas show a high tendency for hemorrhage and apoplexy, which may be the presenting symptom in about a third of the patients [74, 75]. Silent corticotroph adenomas tend to arise in patients older than those with Cushing's disease [75] and clinically more aggressive with higher rates of recurrence [74, 76].

Two types of silent corticotroph adenomas have been described according to their histopathological features [74, 77]. The silent corticotroph adenoma subtype I is morphologically indistinguishable from densely granulated functioning corticotroph adenomas [74, 77]. The silent corticotroph adenoma subtype II is histologically amphophilic and sparsely granulated [74, 77]. The clinical significance of the distinction of these two subtypes is not well established [74, 78].

Thyrotroph Adenomas

Clinical Features Thyrotroph adenomas (thyrotrophinomas, TSH-secreting adenomas) are the least frequent pituitary adenomas representing less than 2% of all tumors [79–82]. Most thyrotroph adenomas are sporadic with only a minority being part of a hereditary syndrome such as MEN1 [83]. Clinically, these tumors may present with inappropriately elevated TSH levels and hyperthyroidism; less frequently tumors may arise in the setting of clinically euthyroid patients and considered as "silent" adenomas [84, 85]. Most tumors are invasive macroadenomas [80, 84].

Histopathology Thyrotroph adenomas are frequently chromophobic at light microscopy and composed of elongated, angular, or irregular cells. Some degree of stromal desmoplasia is commonly seen within the tumors which causes a slight firm consistency [79]. Immunohistochemical analysis usually reveals variable β-TSH positivity; α-subunit (α-SU) of the glycoproteins is also commonly positive. Some tumors may also express GH and PRL with no significant clinical manifestations [80, 85]. Similar to other tumors from acidophilic lineage, thyrotroph adenomas express the Pit-1 transcription factor in addition to the GATA-binding protein 2 (GATA2) [84, 86].

Gonadotroph Adenomas

Clinical Features Gonadotroph adenomas (Fig. 9.4) (gonadotropin-secreting adenomas) are adenomas that secrete the gonadotropins Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH). Unlike other secreting adenomas, gonadotroph adenomas do not usually cause a clinical syndrome related to hormone overproduction; hormonal production from these tumors is inefficient and the detection of excess hormone levels is challenging. Typically these adenomas present as clini-

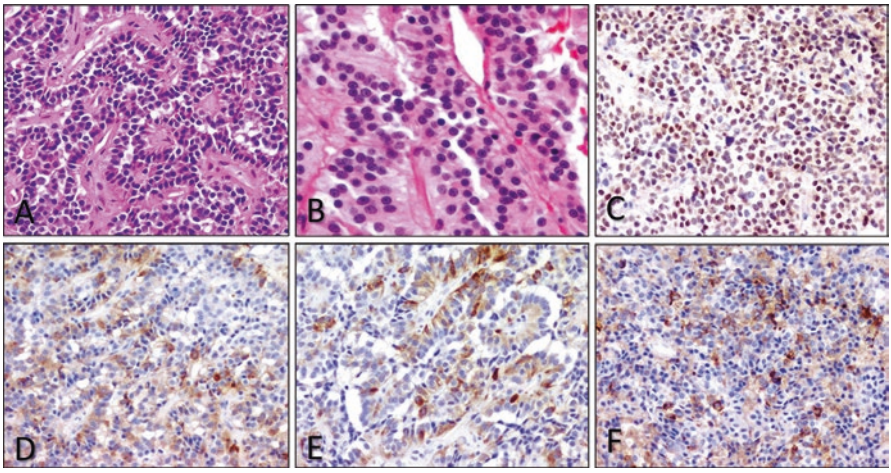

Fig. 9.4 Gonadotroph adenomas. (**a**, **b**) Gonadotroph adenomas are characteristically chromophobic tumors composed of elongated cells that may be arranged in perivascular papillary formations or rosette-like structures. (**c**) These adenomas express the transcription factor steroidogenic factor (SF-1) that regulates gonadotroph differentiation. (**d**–**f**) Combinations of β-FSH (D), β-LH (E), and α-subunit (**f**) are expressed by the adenomas (**a**, **b** H&E; **c** SF-1 IHC; **d** β-FSH IHC; **e** β-LH IHC; **f** α-subunit IHC)

cally nonfunctioning tumors with symptoms related to local mass effects including visual deficits, hypopituitarism, headaches, and cranial nerve palsies [87, 88]. Clinically functioning gonadotroph adenomas are extremely rare and patients may present with menstrual irregularities and puberty abnormalities [89].

Gonadotroph adenomas account for a large proportion of clinically nonfunctioning adenomas (40–60%) [2, 46, 90] and about 20–30% of all adenomas [2]. They are most frequent in the sixth decade and older, and have a slight male predominance [30, 91].

Histopathology Most gonadotroph adenomas are composed of chromophobic cells with nucleus displaying a fine chromatin pattern. The tumor cells may be arranged in a diffuse pattern, but a distinct papillary arrangement of tumor cells is commonly seen in these tumors [87]. The papillary structures are characterized by elongated cytoplasmic processes around blood vessels, in a pattern resembling perivascular pseudorosette formation.

The most pertinent criterion for the diagnosis of gonadotroph adenomas is based on the immunohistochemical findings. Monoclonal antibodies to specific β-FSH, β-LH, and α-SU are recommended for the immunohistochemical characterization of these tumors since they may demonstrate varying degrees of expression for one or more of the gonadotropin subunits. Immunoreactive cells can be scattered throughout the adenoma, but are often clustered. Immunoreactivity for β-FSH tends to be more frequent with stronger and broadly distributed pattern than the other glycoproteins [87]. Gonadotroph adenomas arise from steroidogenic

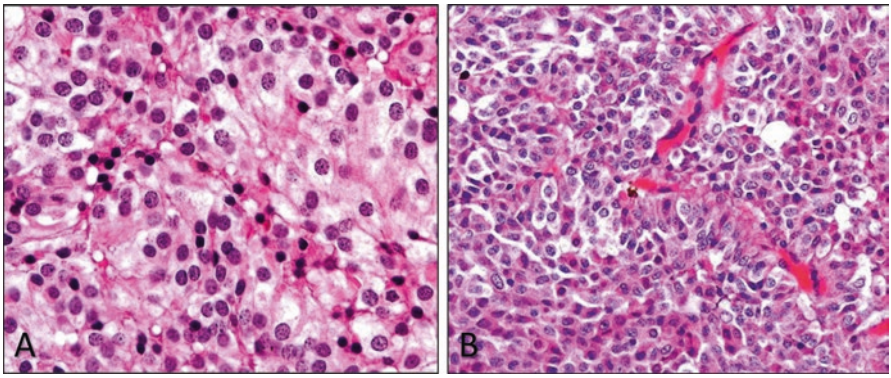

Fig. 9.5 Null cell adenomas. (**a**, **b**) These adenomas are typically chromophobic (**a**), but they may also be oncocytic as a result of mitochondrial accumulation (**b**), a finding of no clinical importance. Null cell adenomas are immunonegative for all pituitary hormones and transcription factors (**a**, **b** H&E)

factor 1 (SF-1) lineage adenohypophysial cells, and they express SF-1 by immunohistochemistry [46].

Null Cell Adenomas

Clinical Features Approximately 20% of adenomas show neither clinical nor immunohistochemical evidence of hormone production [30, 92]. The term "null cell adenoma" is reserved for tumors that lack expression of pituitary hormones and transcription factors by immunohistochemical assays [92]. Null cell adenomas (Fig. 9.5) show clinical presentation of mass lesion with signs of tumor compression of the pituitary and surrounding tissues [30, 92]. The tumors most commonly arise in post-menopausal females and elderly males. The great majority of null cell adenomas are macroadenomas at presentation.

Histopathology Null cell adenomas are chromophobic at light microscopy and tumor cells can be arranged in several neuroendocrine patterns including trabeculae, papillary arrangements, and diffuse pattern. Oncocytic change can be seen in a percentage of cases [93].

As commented above, the adenomas lack immunoreactivity for any of the pituitary hormones (ACTH, PRL, GH, β-TSH, β-FSH, β-LH and α-SU) and transcription factors (Tpit, Pit-1, SF-1) [46, 94]. They are also known as "immunonegative" adenomas. Null cell adenomas are immunoreactive for neuroendocrine markers chromogranin A and synaptophysin, and may be negative for cytokeratin. They may show higher Ki-67 labeling indices compared to gonadotroph adenomas [94]. By ultrastructural analysis, null cell adenomas demonstrate poorly developed organelles in association with only sparse small secretory granules [50]. Large numbers of mitochondria are seen in the tumors with oncocytic degeneration [50, 93].

Plurihormonal Adenomas

Clinical Features Plurihormonal adenomas are rare adenomas that produce more than one pituitary hormone. Due to the rarity of such tumors, their clinical presentation is not well characterized. Some of the adenomas may be clinically nonfunctioning with patients having symptoms of mass effect due to the large size of the adenomas at the time of diagnosis. Rarely, clinically functioning may have endocrine syndromes such as the GH/PRL/TSH-secreting adenomas presenting with acromegaly and thyroid dysfunction. Adenomas may also have unusual immunohistochemical combinations that are unrelated with normal cytogenesis and development of the anterior pituitary [95]. Adenomas with combinations of GH and PRL, or FSH and LH are not considered plurihormonal in this sense [95].

In this category of tumors, the best characterized adenoma is the *Pit-1 positive plurihormonal adenoma* (previously termed "silent subtype III adenoma") [96–99].

Pit-1-Positive Plurihormonal Adenoma These rare adenomas have a slight female predilection and significant prevalence in younger patients [90, 97]. Most Pit-1-positive plurihormonal adenomas are clinically silent, but a minority of patients can show signs of acromegaly, hyperprolactinemia, or hyperthyroidism [96–99].

Histologically, these tumors may be chromophobic adenomas and characteristically express the transcription factor Pit-1 by immunohistochemistry. The tumors may show variable immunoreactivity for GH, PRL, β-TSH, and α-SU [97–99]. Rarely, ACTH expression may also be present [97].

Pit-1-positive plurihormonal adenomas have a typical ultrastructural appearance with sparsely granulated cells harboring characteristic intranuclear inclusions called "spheridia" [97, 98]. Therefore, electron microscopy may be useful for confirmation of the diagnosis.

Tumor Grading

In the previous edition of the WHO Tumor Classification of Endocrine Organs (2004) [100], the pituitary neuroendocrine tumors were divided into *typical adenoma*, *atypical adenoma*, and *carcinoma*. The majority of pituitary neuroendocrine tumors are typical adenomas with bland histological features, infrequent mitotic figures, and a low Ki-67 proliferative index (less than 3%). Atypical adenomas were defined as adenomas with histological features suggestive of an aggressive clinical behavior including elevated mitotic index and a Ki-67 labeling index greater than 3%, and overexpression of the p53 protein by immunohistochemistry [100]. Using these criteria, the incidence of atypical adenoma is relatively variable (2–15%) [2, 101, 102], and its prognostic value not yet established despite more than 10 years of classification. In the upcoming WHO classification [31], the term *atypical adenoma* is no longer recommended. However, assessment of the tumor proliferative potential by mitotic count and Ki-67 index, in addition to other clinical parameters such as tumor invasion (by MRI studies and/or intraoperative impression), is strongly recommended in individual cases for consideration of clinically aggressive adenomas [103–105].

As discussed in the previous sections, some subtypes of adenomas do show an aggressive behavior and patients with such tumors should be carefully followed clinically. These include the sparsely granulated somatotroph adenoma, the Crooke's cell adenoma, the silent corticotroph adenoma, and the plurihormonal Pit-1 positive adenoma (previously known as silent subtype III).

Pituitary Carcinoma

Clinical Features Pituitary carcinomas are very rare, comprising less than 1% of all pituitary neoplasms [2]. By definition, pituitary carcinomas are characterized by demonstration of either craniospinal dissemination or systemic metastases [106]. The majority of cases are hormonally active tumors; the most common are PRL-secreting tumors, followed by ACTH-secreting [107, 108]. Clinically nonfunctioning carcinomas constitute about 15–20% of the cases including gonadotroph, silent corticotroph, and rarely null cell carcinomas [107, 108].

The clinical course of pituitary carcinomas is quite variable. Only rarely carcinomas present with metastases concurrent with the initial sellar tumor, an event suggesting de novo malignancy [109, 110]. The majority of cases have an initial course indistinguishable from that of an ordinary pituitary adenoma, although with multiple local recurrences over a long course prior to metastatic dissemination [107, 108]. Reported periods of latency between presentation of the sellar tumor and metastases vary greatly, ranging from months to years, with a mean reported as 6 years [111]. The latency period appears to have some variation according to the type of adenoma, with reported lower latency period among PRL-secreting tumors in comparison with ACTH-secreting tumors (4.7 versus 9.5 years, respectively) [111].

The mechanisms of progression of pituitary adenoma to carcinoma are not yet totally understood. Although most of the pituitary adenomas are benign tumors, they are frequently invasive into the adjacent structures leading to high level of recurrence. A proliferative continuum from benign adenoma to invasive adenoma to carcinoma has not been demonstrated in the great majority of tumors. The propensity of pituitary adenomas to infiltrate locally and invade adjacent structures appears to be independent of histologic features of the tumors, in that the great majority of invasive adenomas (Fig. 9.6) do not progress to carcinomas. Although both clinically functioning and nonfunctioning adenomas may present as invasive tumors, gross invasion appears to be more frequent in clinically functioning tumors [3], a trend also seen in pituitary carcinomas [107, 108, 111].

Histopathology As commented above, the diagnosis of pituitary carcinoma is dependent on the demonstration of metastatic spread. There are no morphologic criteria to distinguish locally aggressive or even markedly atypical adenomas from pituitary carcinomas when the tumor is still confined to the sella turcica. Morphologic features associated with malignancy including hypercellularity, nuclear and cellular

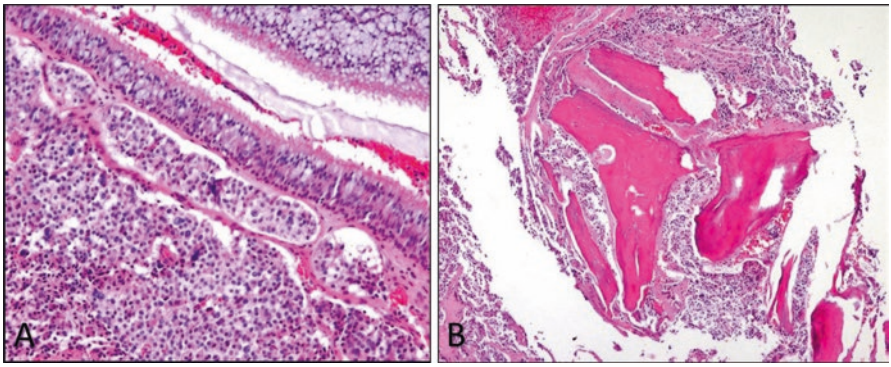

Fig. 9.6 Invasive adenomas. (**a**, **b**) A large number of pituitary adenomas invade the surrounding anatomic structures including the sphenoid sinuses (**a**) and bone (**b**). Adenoma invasiveness is considered a predictor for tumor recurrence (**a**, **b** H&E)

pleomorphism, increased mitotic activity, necrosis, and dural/bony invasion are commonly present but are not necessarily diagnostic of carcinoma.

Mitotic activity varies considerably in primary tumors that have progressed to carcinoma; a mean of 2.5 mitoses/10 HPF was reported in one large series [111]. In general, metastatic lesions tend to demonstrate greater degree of cytologic atypia and increased mitotic activity, the mean value of 6 mitoses/10 HPF reported in the previous study [111]. Similarly, Ki-67 labeling indices of the sellar tumors are quite variable and show considerable overlap with ordinary pituitary adenomas. However, they are often higher in metastatic deposits. Additionally, unlike pituitary adenomas, carcinomas appear to show overexpression of the p53 protein by immunohistochemistry [28], but mutations of the *TP53* gene are rare [28].

Pituitary Blastoma

Clinical Features Pituitary blastoma is a rare primitive malignant neoplasm of the pituitary gland that occurs mostly in the pediatric population, first described by Scheithauer et al. [112]. About 20 cases have been reported in the literature [17, 18, 112–114]. The majority of the cases arise in infants younger than 24 months of age (median 8 months) [18], with a slight female predominance [18]. In about two-thirds of the cases, signs and symptoms of Cushing's syndrome are reported, followed by ophthalmoplegia [18]. Overall prognosis is poor with 40% death in the first 26 months (median 8 months) after diagnosis reported in the largest series [18].

Pituitary blastoma has been recently incorporated as part of the DICER1 syndrome, or pleuropulmonary blastoma (PPB)-familial tumor and dysplasia syndrome, caused by heterozygous germ-line mutations in the *DICER1* gene [17, 18].

Histopathology Morphologically, the tumors are composed of three major elements including Rathke-type epithelial glands or rosette-like formations intermixed with small primitive-appearing cells and larger secretory epithelial cells [112, 113]. The cells are immunoreactive for neuroendocrine markers like synaptophysin and chromogranin. The majority of the tumors expressed ACTH, and a few cases were reported to express GH in a subset of cells [18]. Proliferative index is variable with Ki-67 labeling ranges from low to highly elevated grades [18]. Moreover, a straight correlation between Ki-67 index and prognosis has not been established.

Pituitary Non-neuroendocrine Tumors

Introduction

Although much less frequent than pituitary adenomas, non-neuroendocrine tumors arising in the pituitary are intrinsic tumors of the gland that are important in the differential diagnosis of sellar masses (Table 9.1). The main entities considered in this group of tumors and discussed in this chapter are the *pituicytomas*, the *granular cell tumors of the neurohypophysis,* and the *spindle cell oncocytomas*.

All three tumors are low-grade, non-neuroendocrine neoplasms of the sella that can clinically and radiologically mimic nonfunctioning pituitary adenomas. Patient's clinical presentation is mostly related to tumor size, with signs and symptoms of compression of adjacent structures and the pituitary stalk including visual disturbances, headaches, hyperprolactinemia and amenorrhea, and fatigue [115]. Only a minority of the tumors may present with diabetes insipidus [115].

Pituicytoma has been used to describe a number of tumors in the region of the sella including pilocytic astrocytomas and granular cell tumors. In 2000, Brat and colleagues formally defined pituicytoma as a distinctive low-grade glial neoplasm that arises from pituicytes [116]. Pituicytes are the specialized glia of the neurohypophysis and pituitary stalk that have a sustentacular function in the posterior pituitary.

Granular cell tumors of the neurohypophysis, unlike those tumors located in gastrointestinal tract and skin that are believed to be of Schwann cell origin are considered to be unique neoplasms of the neurohypophysis and pituitary stalk, and have also been suggested to derive from pituicytes [117].

Spindle cell oncocytomas were first described in 2002 by Roncaroli and colleagues as non-endocrine neoplasms characterized by mitochondria-rich, spindle to epithelioid cells [118]. Although these authors have proposed a folliculostellate cell origin based on similarities of their ultrastructural and immunohistochemical features [118], recent data on the shared TTF-1 immunoreactivity of pituicytomas, granular cell tumors, and spindle cell oncocytomas [119, 120] may suggest more similarity in origin than was originally suspected (see below).

The specialized glia of the neurohypophysis and pituitary stalk, the pituicyte, is embryologically derived from the floor of the diencephalon. Recent data have shown that the floor of the diencephalon is an area under the influence of the thyroid

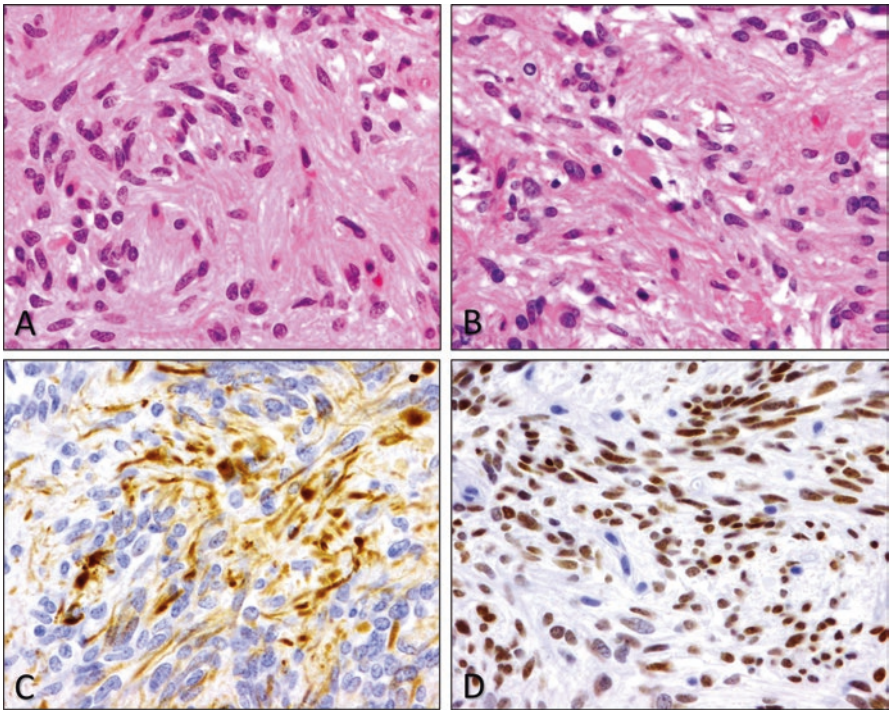

Fig. 9.7 Pituicytoma. (**a**, **b**) Pituicytomas are composed of elongate, elongated cells arranged in fascicles, in a pattern resembling pilocytic astrocytoma. Unlike the latter, pituicytomas lack the characteristic Rosenthal fibers, but eosinophilic granular bodies may be seen (**b**). (**c**) The tumor cells are variably immunoreactive for GFAP and strongly reactive for TTF-1 (**d**) (**a**, **b** H&E; **c** GFAP IHC; **d** TTF-1 IHC)

transcription factor-1 (TTF-1), a transcription factor known to be critical for the development of lungs and thyroid, and now revealed to play a role in the induction of the infundibular anlage during development of the posterior pituitary and infundibulum [119]. Similar to the developing and normal pituicytes, these three tumors – pituicytomas, granular cell tumors and spindle cell oncocytomas – show diffuse nuclear expression for TTF-1 [119, 120]. On the other hand, folliculostellate cells, the sustentacular cells of the adenohypophysis, do not express TTF-1 [120].

Furthermore, the ultrastructural morphology of these tumors shows similarities with the described variants of normal pituicytes, another indication of a possible common pituicyte-lineage [120]. Pituicytes have five distinct ultrastructural variants: light (or major), dark, granular, ependymal, and oncocytic [121]. The current hypothesis is that these non-endocrine pituitary tumors would originate from specific variants of pituicytes, i.e., pituicytomas from the light/major variant, granular cell tumors from the granular variant, and the spindle cell oncocytomas from the oncocytic variant [117, 120, 122, 123].

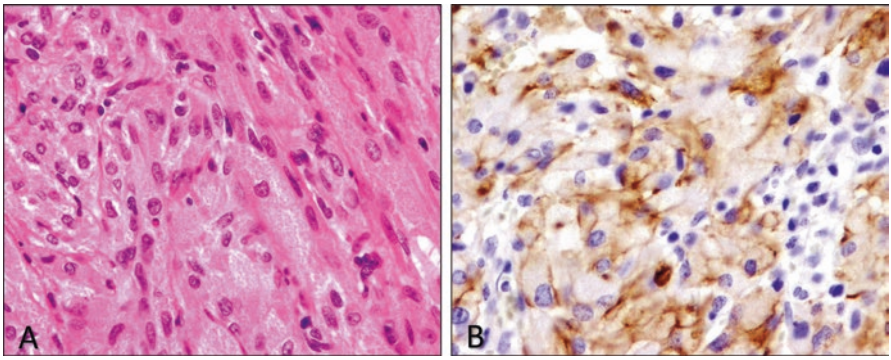

Fig. 9.8 Granular cell tumor. (**a**) Granular cell tumors are characterized by large polygonal cells with abundant granular cytoplasm. (**b**) Similar to pituicytomas, these tumors are variably immunoreactive for GFAP (**a** H&E; **b** GFAP IHC)

Specific Characteristics of the Tumors

Pituicytoma

Clinical Features Pituicytomas (Fig. 9.7) are rare tumors, the majority of the tumors involving adults (fifth and sixth decades), with a slight male predominance [122].

The tumors are usually well-circumscribed, solid intrasellar lesions with suprasellar extension. Neuroimaging findings are not specific and may be mistaken for pituitary adenomas. Due to the rarity of these tumors, their precise clinical behavior is not well-known. The majority of the cases reported appear to behave as low-grade tumors, with some tendency for recurrence after subtotal excision [122].

Histopathology Pituicytomas are grossly soft, tan lesions indistinguishable from pituitary adenomas. Morphologically, the tumors are composed of elongate, fibrillary cells arranged in fascicles, in a pattern that resembles pilocytic astrocytoma. However, unlike pilocytic astrocytoma, most tumors lack biphasic histological pattern and characteristic Rosenthal fibers and eosinophilic granular bodies [116]. Mitotic activity is mostly absent, and Ki-67 labeling index is generally low.

By immunohistochemistry, pituicytomas do not show any immunoreactivity for neuroendocrine markers (chromogranin, synaptophysin) or for pituitary hormones [116, 118, 120]. The tumor cells are typically immunoreactive for vimentin and S-100 protein. Although GFAP is strongly positive in many cases, the stain can be variable and even absent [116, 118]. Focal EMA immunoreactive may be present [116, 120]. As mentioned above, pituicytomas are characteristically strongly immunoreactive for TTF-1 [119, 120].

Ultrastructural features include spindle cells with abundant intermediate filaments and lack of neurosecretory granules. There is no pericellular deposition of basal lamina-like material like that seen in schwannomas, and only scattered

intercellular junctions. These characteristics are similar to those seen in the so-called major pituicytes, the most common type of normal pituicytes that are reminiscent of astrocytes [121].

Granular Cell Tumor of the Neurohypophysis

Clinical Features The majority of the granular cell tumors (Fig. 9.8) (GCTs) are microscopic lesions found incidentally at autopsy. Symptomatic tumors are quite rare, corresponding to less than 0.5% of tumors involving this region [115]. GCTs arise in a wide range of age distribution, but most symptomatic tumors are diagnosed in the fourth or fifth decade of life, with a 2:1 predominance of females [115, 117]. In general, these tumors are slow-growing, benign neoplasms; however, a few cases of tumors with more aggressive behavior have been reported [117]. Patient outcome has been correlated with extension of surgical resection or combination of surgery and radiation therapy [117]. Like pituicytomas and spindle cell oncocytomas, GCTs may be very vascular and may bleed extensively during surgical exploration [124].

Histopathology GCTs are characterized by proliferation of large, polygonal cells arranged in sheets or small lobules surrounded by fine capillaries. The cells have a distinct eosinophilic cytoplasm with fine to coarse granularity. The nuclei are round with delicate chromatin and uniform nucleoli, and tend to be located in the periphery of the cells. The cytoplasmic granules are positive for PAS and diastase-resistant. The tumor shows absent to low mitotic activity, and necrosis is rarely seen.

Granular cell tumors are diffusely immunoreactive for vimentin and S100 protein, but only occasionally immunoreactive for GFAP [117, 120]. The macrophage/lysosome marker CD68 is consistently and strongly immunoreactive in all tumors. The tumors are negative for neuroendocrine markers. Most significantly, GCTs are strongly immunoreactive for TTF-1 as the other pituicyte-derived tumors [119, 120].

Electron microscopy shows characteristically abundant membrane-bound, electron-dense material in the cytoplasm, consistent with lysosomes. Intermediate filaments are scarce, and neurosecretory granules are absent [120].

Spindle Cell Oncocytomas

Clinical Features Similar to the tumors discussed above, spindle cell oncocytomas (Fig. 9.9) (SCOs) are a rare primary tumor of pituitary gland with approximately 30 cases reported in the literature [123, 125]. All lesions currently reported have arisen in adults (mean of 56.4 years) and have equal distribution between genders [125]. The majority of the reported cases have a benign clinical course; however, recurrence has been reported in about a third of the reported cases [125]. A few cases with more aggressive clinical course have also been described [123, 126].

Histopathology SCOs are characterized by spindle cells arranged in interwoven fascicles intermixed with plump cells with eosinophilic, finely granular cytoplasm consistent with an oncocytic cellular component. Mild to moderate cellular atypia

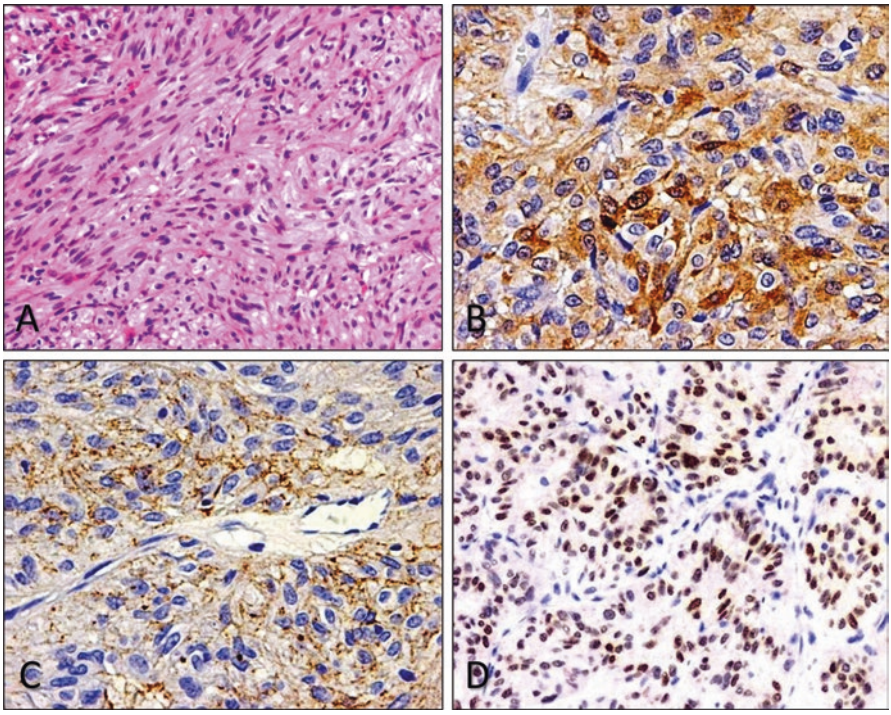

Fig. 9.9 Spindle cell oncocytoma. (**a**) Oncocytic plump and spindle cells are arranged in interlaced fascicles in spindle cell oncocytomas. The tumor cells are strongly immunoreactive for S100 (**b**), EMA (**c**), and, similar to the other pituicyte-derived tumors, are also immunoreactive for TTF-1 (**d**) (**a** H&E; **b** S100 IHC; **c** EMA IHC; **d** TTF-1 IHC)

can be seen. Mitotic activity is frequently low, although it can be increased in recurrent lesions [123].

The tumors lack immunoreactivity for neuroendocrine markers and pituitary hormones; they are immunoreactive for EMA, vimentin, S-100, mitochondria antibody (MU213-UC clone 131-1), galectin-3, and only focally for GFAP [120, 123]. As commented above, SCOs show diffuse nuclear expression for TTF-1 [119, 120].

A key characteristic of SCOs, as revealed by its name, is the presence of abundant accumulation of mitochondria by ultrastructural analysis. Tumor cells lack secretory granules, junctional complexes and basal-like membrane [123].

Craniopharyngioma

Clinical Features Craniopharyngiomas (Fig. 9.10) represent 1–2% of all intracranial neoplasms and about 10% of the tumors of the sellar region [1, 127]. The tumors are more frequent in children and adolescents (5–15 years of age), in whom

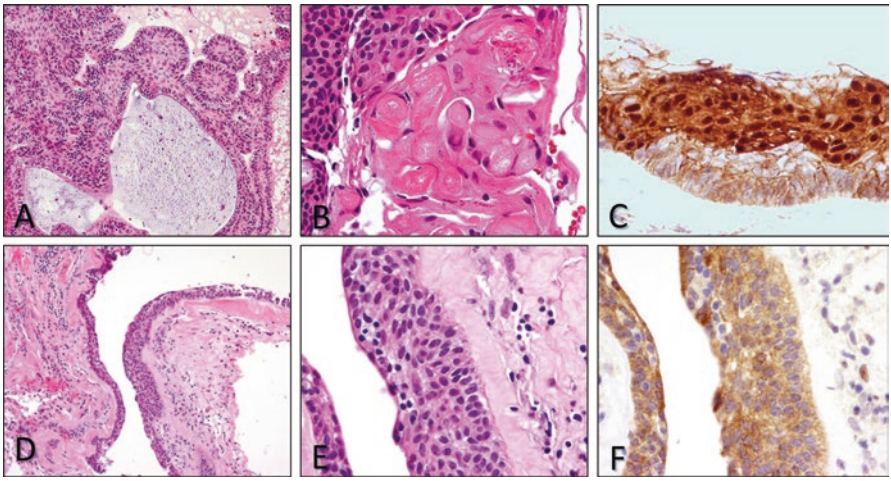

Fig. 9.10 Craniopharyngioma. (**a**–**c**) Adamantinomatous craniopharyngioma typically shows a pseudostratified epithelium with a palisading arrangement of the basal cells (**a**) with formation of ghost-like cells also called "wet" keratin (**b**). (**c**) Nuclear reactivity for β-catenin reiterates the main molecular genetic alteration in adamantinomatous craniopharyngiomas, mutations on the CNTTB1 gene. (**d**–**f**) Papillary craniopharyngioma is composed of pseudostratified epithelium surrounding fibrovascular cores (**d**). Flaky or wet keratin is not seen in these tumors. (**f**) Immunostaining for the BRAF V1 antibody emphasizes the BRAF V600E mutation present in these tumors (**a**–**c** H&E; **d** β-catenin IHC; **a**, **b** H&E; **c** BRAF IHC)

they represent about 10% of all intracranial neoplasms [1, 127, 128]; but, a second smaller peak incidence is observed in the fifth and sixth decades (45–60 years) [1, 127]. The majority of the tumors are suprasellar, although tumors may have an intrasellar component and some arise entirely beneath the sellar diaphragm [128]. Large tumors may show growth in the parasellar region and into brain.

Two variants of craniopharyngiomas are recognized clinically and histologically – the *adamantinomatous* and the *papillary craniopharyngioma* [127]. The adamantinomatous craniopharyngiomas are commonly seen in the pediatric population, while papillary craniopharyngiomas arise more frequently in adults [127]. The two histologic variants can also be distinguished from each other on neuroimaging basis [129]. Adamantinomatous craniopharyngioma is a predominantly cystic, lobulated mass with cyst fluid frequently hyperintense on T1WI due to the cholesterol content and with foci of calcification. Papillary craniopharyngiomas tend to manifest as predominantly lobulated rounded masses and cysts, when present, are hypointense in T1WI, reflecting less complex contents [129]. Both variants of craniopharyngiomas are histologically classified as grade I tumors [127]; however, significant morbidity and recurrence rates as high as 20% are seen in particular in cases with subtotal surgical resection [127].

Recently, the description of distinct genetic mutation pathways harbored mutually exclusively by the two variants of craniopharyngiomas has substantiated the idea that they represent distinct tumor subtypes. Activating mutations of the

CTNNB1 gene, that encodes β-catenin, are present in the great majority of adamantinomatous craniopharyngiomas [130–132]. This mutation results in aberrant nuclear accumulation of β-catenin protein [133] and WNT pathway activation. On the other hand, *BRAF* mutations (BRAF V600E) have been reported as the main oncogenic alteration in papillary craniopharyngiomas [131]. The description of mixed tumors with both BRAF V600E and CTNNB1 mutations, although a rare event, has been reported [134].

Adamantinomatous Craniopharyngiomas The tumors are grossly characterized by cystic formations containing a viscous admixture of glistening birefringent cholesterol crystals and calcific desquamated debris that gives a characteristic "machinery oil" appearance to the contents. Histologically, the cystic formations are composed of stratified epithelium with a palisading arrangement of basal cells, intermixed with nodular strands of solid and cystic epithelium. Secondary degenerative changes of the epithelium lead to the formation of laminated masses of keratin, known as "wet keratin," that tend to become confluent and undergo calcification. These nodular masses of "wet keratin" are especially distinctive and diagnostic of craniopharyngiomas. In addition to epithelial components, extensive fibrosis, chronic inflammation, and cholesterol clefts with a giant-cell reaction may be prominent. In addition to several cytokeratins immunoexpression [135], strong nuclear β-catenin positivity in tumor cells is a reliable marker for the diagnosis of adamantinomatous craniopharyngioma [133].

Papillary Craniopharyngiomas The tumors are circumscribed masses and lack the typical cysts with calcification and "machinery oil" cyst content seen in adamantinomatous tumors. Histologically, the tumor consists of well-differentiated, squamous-lined papillae surrounding cores of fibrovascular stroma. The squamous-like epithelium lacks true keratin formation and keratohyalin granules, thereby differing from epidermoid and dermoid cysts. The tumors do not possess the columnar palisading, microcystic degeneration, keratinous nodules, and cholesterol clefts that are so characteristic of the adamantinomatous variant. Papillary craniopharyngiomas express strong cytoplasmic staining with the monoclonal antibody specific to the BRAF V600E mutation (VE1) [136, 137], an important tool in the differential diagnosis of this entity with Rathke's cleft cyst with squamous metaplasia [136, 137].

Craniopharyngiomas are generally well-circumscribed lesions but they are not encapsulated and are often adhered to adjacent structures. An exuberant gliotic reaction of the surrounding brain parenchyma at the tumor–brain interface may be present. However, mitotic figures and other features of histologic aggression, aside from focal invasion, are rarely seen [127].

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Surgical Anatomy of the Sellar Region

10

Nathan T. Zwagerman, Stefan Lieber,
and Juan C. Fernandez-Miranda

Introduction

In addressing pathology of the sellar region, several approaches have been used, and a detailed knowledge of the associated anatomy is critical for successful surgery and to avoid complications. This chapter will address the anatomy of this region in a logical and detailed manner, focusing on specific approaches to the region and describing potential pitfalls associated with them. In addition, this chapter will describe the critical neurovascular structures associated with this area as a helpful guide when exploring not only the sella but also the perisellar space, which includes the cavernous sinus, suprasellar, and interpeduncular cistern.

Sphenoid Bone

The foundation of the sellar anatomy begins with knowledge of the sphenoid bone (Fig. 10.1). The sphenoid bone forms the sella turcica, which allocates the pituitary gland. As a result, this bone is of critical importance for surgical approaches to the sellar region. Given its central location, it is also associated with many neurovascular structures in the region.

The anterior view of the sphenoid bone consists of a central portion called the body, the lesser wings, which sprout from the superior portion of the body, and the greater wings, which sprout from the inferior portion (Fig. 10.1a). Between the greater

N.T. Zwagerman, MD • S. Lieber, MD • J.C. Fernandez-Miranda, MD (✉)
Department of Neurological Surgery, University of Pittsburgh
Medical Center, Pittsburgh, PA, USA
e-mail: fernandezmirandajc@upmc.edu

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_10

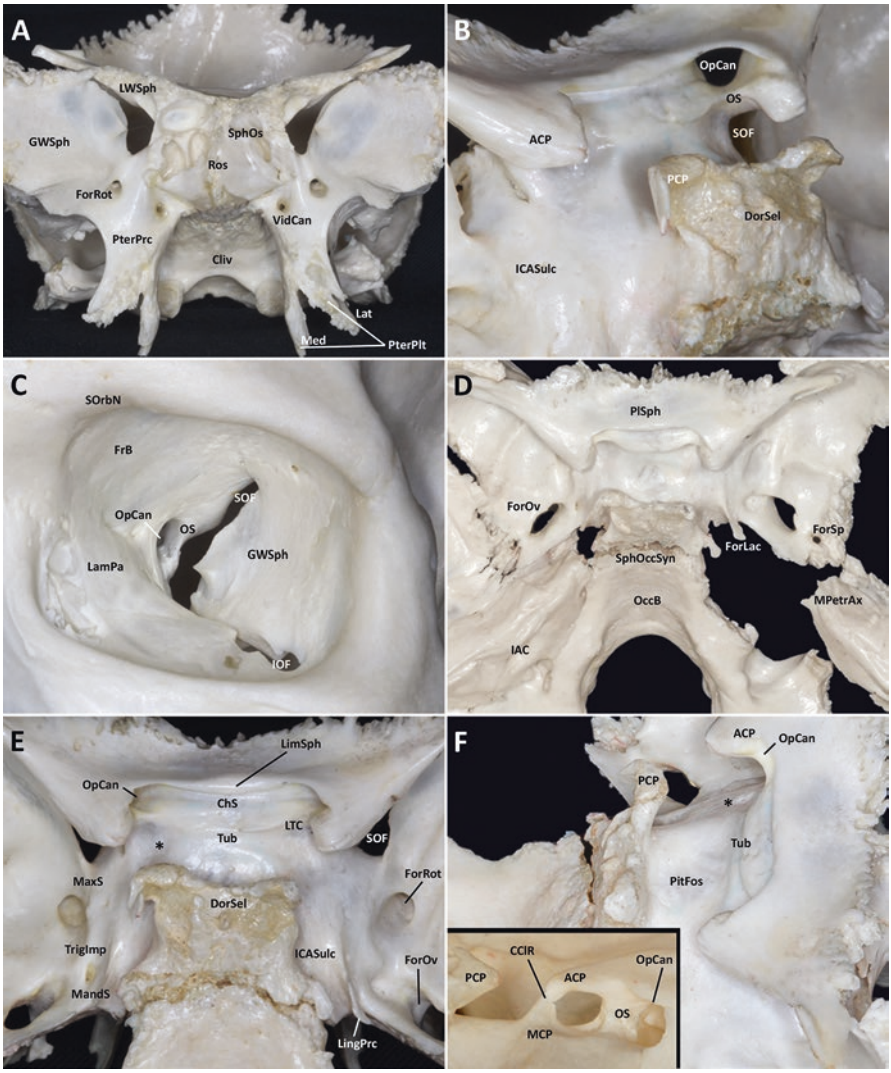


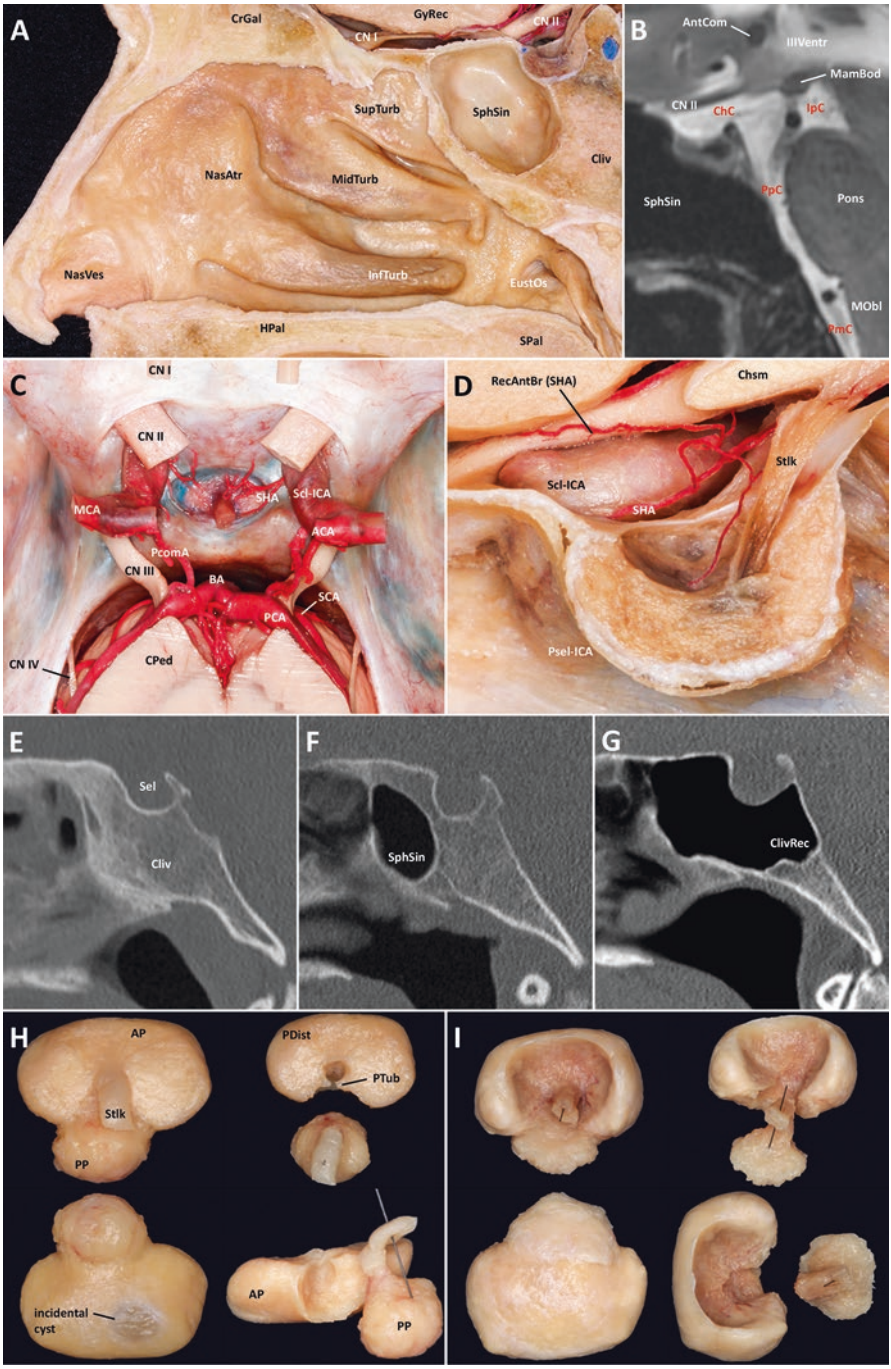
Fig. 10.1 Osseous anatomy. (**a**) anterior view; (**b**) antero-oblique view into the pituitary fossa; (**c**) right orbit; (**d**) superior view onto the skull base, the right petrous bone is displaced laterally to demonstrate the structures forming the foramen lacerum; (**e**) detailed anterior view into the pituitary fossa; (**f**) lateral view into the pituitary fossa, demonstrating the varying morphology of the middle clinoid process (MCP). The asterisk shows the localization of the MCP when present (infero-laterally to the LTC). The insert demonstrates the carotico-clinoidal ring that is formed by the fusion of the anterior and middle clinoid processes. (**a**–**f**: dry, macerated skull specimen). *GWSph* greater wing of the sphenoid bone, *LWSph* lesser wing of the sphenoid bone, *Ros* rostrum, *SphOs* sphenoid ostium, *Cliv* clivus (occipital bone), *ForRot* foramen rotundum, *VidCan* vidian canal, *Med/Lat PterPl* medial/lateral pterygoid plate, *PterPrc* pterygoid process, *ACP* anterior clinoid process, *PCP* posterior clinoid process, *DorSel* dorsum sellae, *SOF* superior orbital fissure, *OpCan* optic canal, *OS* optic strut, *ICASulc* sulcus of the internal carotid artery, *SOrbN* supraorbital notch, *FrB* frontal bone, *LamPa* lamina papyracea (orbital lamina of the ethmoid bone), *IOF*

and lesser wings, the superior orbital fissure is formed. The vomer (a separate bone) connects with the sphenoidal rostrum inferiorly. The pterygoid process and the lateral and medial pterygoid plates project inferiorly. The body of the sphenoid is shaped like a block and houses the sphenoid sinus. The anterior face of the sphenoid body contains sphenoid ostia, which open into the nasal cavity. The superior parts of the lesser wings form the posterior floor of the anterior cranial fossa, whereas the undersides of the wings form the posterior roof of the orbit. On the medial aspect of the lesser wing, the optic canal is seen and is separated from the superior orbital fissure by the optic strut (Fig. 10.1b, c). The greater wings form the lateral orbital wall and the anterior pole of the middle cranial fossa. The foramen rotundum is located at the junction of the body and the greater wing and transmits the second/maxillary division of cranial nerve V. The greater wing also contains the foramen ovale (third/mandibular division of cranial nerve V) and foramen spinosum (middle meningeal artery) (Fig. 10.1d).

The superior view of the sphenoid bone is dominated by the pituitary fossa located centrally (Fig. 10.1d–g). The fossa is bound posteriorly by the dorsum sellae and anteriorly by the tuberculum sellae. Anterior to the pituitary fossa is the chiasmatic groove connecting the optic canals laterally and bound by the planum sphenoidale anteriorly. The limbus of the sphenoid marks the edge between the planum sphenoidale and the chiasmatic sulcus. The frontal lobe, gyrus rectus, and olfactory tracts rest on the lesser wings and the planum, while the suprasellar cistern and optic chiasm lie above the chiasmatic sulcus. Projecting laterally and posterior along the lesser wing is the sphenoid ridge, which separates the frontal and temporal lobes along the sylvian fissure. The medial edge of the lesser wing continues as the anterior clinoid process, which forms the lateral wall of the optic canal and covers the clinoidal segment of the internal carotid artery (ICA). The posterior clinoid process is located superolaterally on the dorsum sellae. The dorsum sellae is continuous inferiorly with the clival portion of the occipital bone. The carotid arteries lie directly lateral to the sella turcica and form a groove, the carotid sulcus, along their path along the clivus and through the cavernous sinus. A portion of bone may encircle the carotid at the cavernous sinus roof. This bone is an extension of the middle clinoid and is important to note when exposing the carotids for endonasal surgery (Fig. 10.1f). The cavernous sinus encircles the carotid lateral to the sella and forms interdural intercavernous connections around the pituitary gland.

The sphenoid sinus (Fig. 10.2) provides direct access to the sellar region and has a significant amount of variability depending on the extent of pneumatization. The sphenoid sinus has been classified into three types with varying degrees of

Fig. 10.1 (continued) inferior orbital fissure, *PlSph* planum sphenoidale, *IAC* internal auditory canal, *OccB* occipital bone, *SphOccSyn* spheno-occipital synchondrosis, *ForLac* foramen lacerum, *ForOv* foramen ovale, *ForSp* foramen spinosum, *MPetrApx* medial petrous apex, *MS* maxillary strut, *MandS* mandibular strut, *TrigImp* trigeminal impression, *ChS* chiasmatic sulcus, *LingPrc* lingual process (sphenoid bone), *Tub* tuberculum sellae, *LTC* lateral tubercular crest, *LimSph* limbus sphenoidale, *PitFos* pituitary fossa, *MCP* middle clinoid process, * localization of the middle clinoid process when present, *CClR* carotico-clinoidal ring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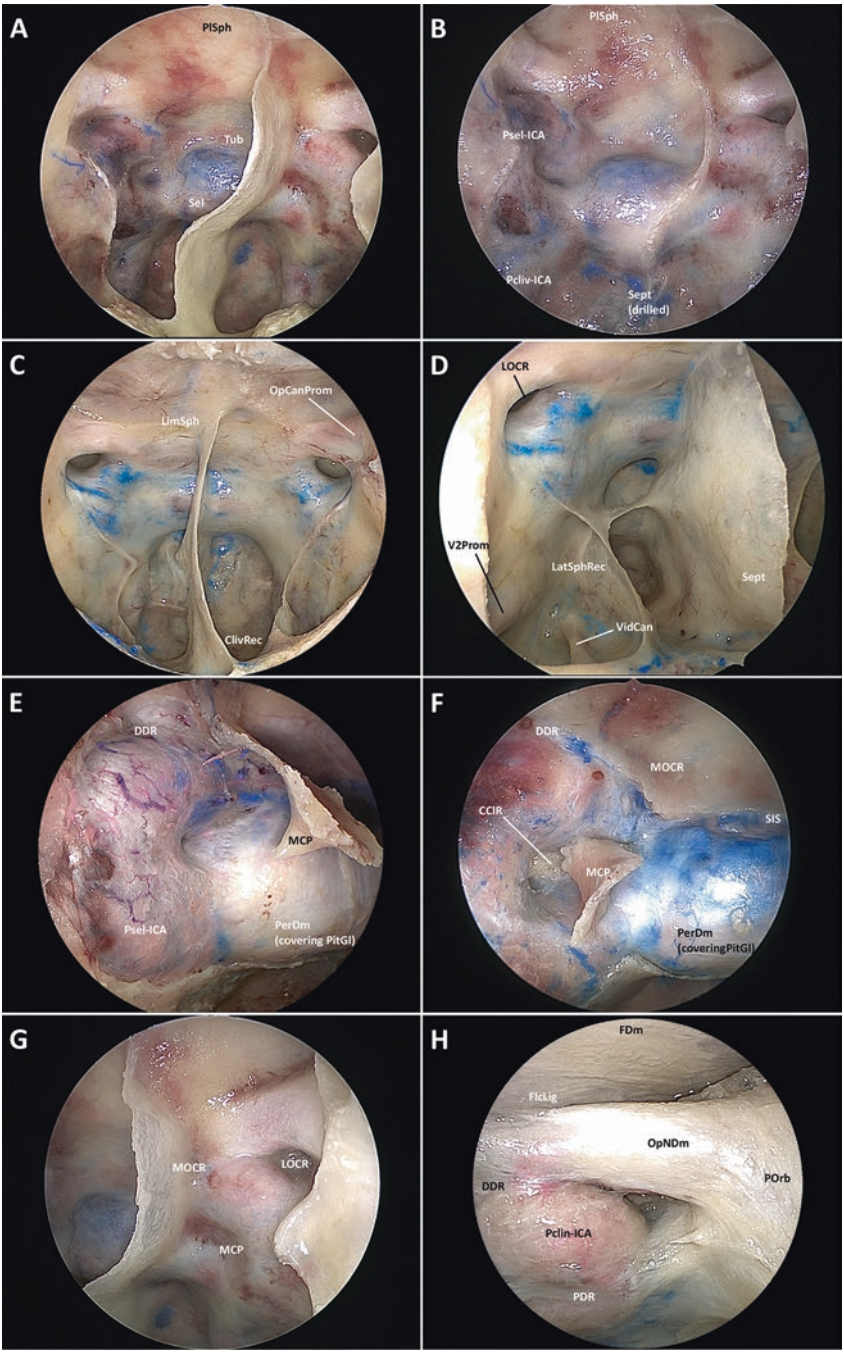
pneumatization: conchal, presellar, and sellar (Fig. 10.2e–g). In the conchal type, there is solid bone with no pneumatization of the sphenoid sinus. In the presellar type, the air cavity does not extend beyond the anterior wall of the sella. The sellar type is described when the air pattern extends below the sella to the clivus. Pneumatization is not complete until adolescence, and the predominant pattern seen in adult patients is the sellar type. Pneumatization may continue with age and the sphenoid sinus may enlarge to the roots of the pterygoid processes forming lateral recesses, which make traversing nerves, such as vidian and V2, easier to identify (Fig. 10.3d). Pneumatization may progress so that the bone overlying critical structures may be dehiscent or absent with no bone between layers of mucosa and dura. Often, septations are encountered within the sphenoid sinus, usually in a paramedian arrangement and therefore causing asymmetric, unequal subcompartments (Fig. 10.3). Many times the septations lead to the paraclival and cavernous carotid arteries, and caution should be applied when removing these structures. The carotid artery typically forms a bony prominence as it ascends the clival region, making it visible from an anterior approach. Likewise, the carotid artery is usually identifiable again at the clinodal segment, just below the lateral opticocarotid recess; this recess represents the optic strut of the anterior clinoid and is variably pneumatized. It also correlates with the floor of the optic canal, which may be visible as osseous prominences lateral to the chiasmatic sulcus. Occasionally, a posterior ethmoid cell (also known as Onodi cell) may limit the view of the superior aspect of the tuberculum or planum as it hides the optic nerve prominence.

Fig. 10.2 Miscellaneous anatomy: pituitary, cisternal space, spenoidal pneumatization. (**a**) nasal anatomy; (**b**) perisellar cisternal spaces; (**c**) cranial nerves and microvasculature of the perisellar region; (**d**) detail of the three "classic" branches of the superior hypophyseal artery; (**e**) conchal; (**f**) presellar; and (**g**) sellar pneumatization of the spenoid sinus. (**h**, **i**) morphological variation between two different pituitary glands, the anterior and posterior lobes have been separated on the right sides respectively. (**a**, **c**–**d**, **h**–**i**: formalin-fixed, silicone injected cadaveric specimen, **b**: sagittal T2-weighted MRI, **e**–**g**: mid-sagittal non-contrast bone-windowed CT). *NasVes* nasal vestibulum, *NasAtr* nasal atrium, *SupTurb* superior turbinate, *MidTurb* middle turbinate, *InfTurb* inferior turbinate, *HPal* hard palate/nasal floor, *SPal* soft palate, *EustOs* ostium of the Eustachian/pharyngotympanic tube, *Cliv* clivus, *SphSin* sphenoid sinus, *CrGal* crista galli, *GyRec* gyrus rectus, *CN I* olfactory nerve (bulb/tract), *CN II* optic nerve, *ChC* chiasmatic cistern, *IpC* interpeduncular cistern, *PpC* prepontine cistern, *PmC* premedullary cistern, *MamBod* mammilary body, *AntCom* anterior commissure, *IIIVentr* third ventricle, *MObl* medulla oblongata, *CN III* oculomotor nerve, *CN IV* trochlear nerve, *MCA* middle cerebral artery, *PcomA* posterior communicating artery, *ACA* anterior cerebral artery, *SHA* superior hypophyseal artery, *Scl-ICA* supraclinoidal internal carotid artery (intradural), *BA* basilar artery, *PCA* posterior cerebral artery, *SCA* superior cerebellar artery, *CPed* cerebral peduncle, *Chsm* optic chiasm, *Stlk* pituitary stalk, *Psel-ICA* parasellar internal carotid artery (extradural), *RecAntBr (SHA)* recurrent anterior branch to the optic nerve (off SHA), *Sel* sella turcica/pituitary fossa, *ClivRec* clival recess, *AP* anterior pituitary/adenohypophysis, *PP* posterior pituitary/neurohypophysis, *PTub* pars tuberalis of the adenohypophysis, *PDist* pars distalis


A
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FDm
FlcLig
OpNDm
DDR
POrb
Pclin-ICA
PDR

Pituitary Gland

When viewing the pituitary gland during surgery, the posterior lobe has a more whitish appearance compared to the more yellowish-colored anterior gland (Fig. 10.2h–i). The pars tuberalis is formed from the anterior gland as it wraps around the lower part of the pituitary stalk [1]. The posterior gland tends to be more adherent to the inferior wall in comparison to the anterior gland and the anterior wall; sometimes the pituitary lobes are separated by small pars intermedia cysts. Due to the osseous encasement, the anterior, inferior, and posterior aspects of the gland are more regularly shaped. The lateral aspects of the gland, however, may vary in shape due to the pliability of the medial walls of the cavernous sinus. The distance between the cavernous carotid artery and the pituitary gland is quite variable and may range from several millimeters to direct contact [2–4]. In rare cases, medially looping ICAs may even deform the gland and cause parts of the gland to be behind, in front of, or below the artery, forming an entity named "shallow sella".

Diaphragma Sellae

A thin layer of connective meningeal tissue covers the pituitary gland and forms the roof of the sella turcica. The pituitary stalk penetrates the diaphragm centrally to enter the pituitary fossa. The diaphragm is rectangular in shape and tends to be convex/concave as opposed to flat and is usually thicker toward the periphery. Renn and Rhoton found that the thickness was similar to one layer of dura in 38% of specimens, whereas 62% of specimens had a significantly thinned area that would likely

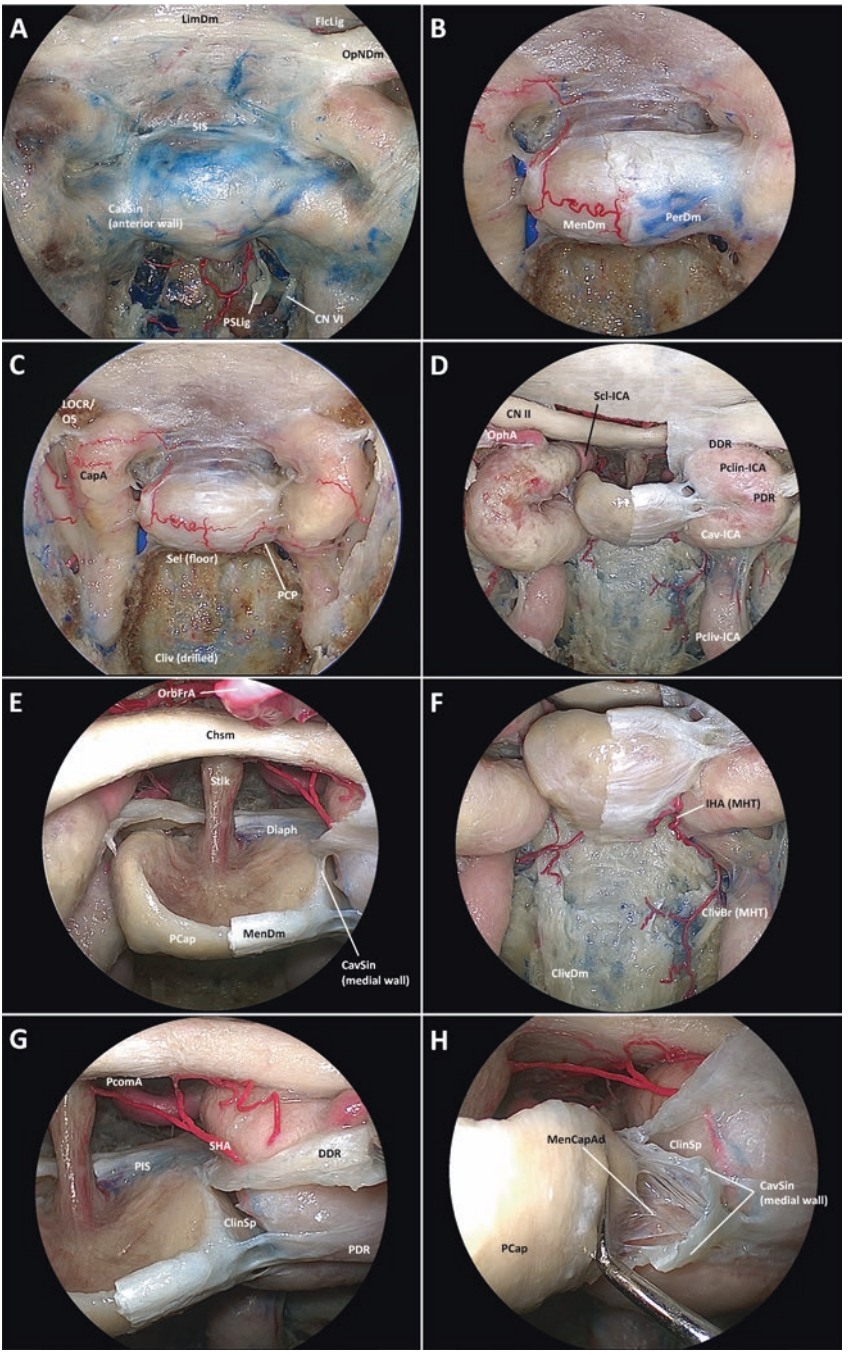
Fig. 10.3 Sphenoidal anatomy and important landmarks. (**a**) wide sphenoidotomy (Reprinted with permission from Zwagerman et al. [17]); (**b**) view from below, the paramedian septations have been drilled flush. (**c**, **d**) morphological variation in a different specimen, the extensive pneumatization allows for visualization of V2 prominence and the vidian nerve coursing in the floor of the lateral sphenoidal recess. (**e**) mobilization of the middle clinoid process (*right side*). (**f**) in comparison shows a carotico-clinoidal ring (see also Fig. 10.1f). (**g**) View into the left sphenoid sinus. The optic strut/lateral opticocarotid recess forms the floor of the optic canal and correlates with the anterior clinoid process from the transcranial perspective (Reprinted with permission from Zwagerman et al. [17]). (**h**) 180° decompression of the optic nerve in its dural sheath, note the space superiorly which is formed by the falciform ligament after bone removal (Reprinted with permission from Zwagerman et al. [17]). (formalin-fixed, silicone injected cadaveric specimen). *PlSph* planum sphenoidale, *Tub*tuberculum sellae, *Sel* sella turcica/pituitary fossa, *Psel-ICA* parasellar internal carotid artery (extradural), *Pcliv-ICA* paraclival internal carotid artery, *Sept* septations within sphenoid sinus, *OpCanProm* optic canal prominence, *LimSph* limbus sphenoidale, *ClivRec* clival recess, *LOCR* lateral opticocarotid recess, *V2Prom* prominence of the maxillary division of trigeminal nerve, *VidCan* vidian canal, *LatSphRec* lateral recess of the sphenoid sinus, *DDR* distal dural ring, *MCP* middle clinoid process, *PerDm* periosteal dura mater, *PitGl* pituitary gland, *MOCR* medial opticocarotid recess, *CClR* carotico-clinoidal ring, *SIS* superior intercavernous sinus, *PDR* proximal dural ring, *FlcLig* falciform ligament, *FDm* frontal dura mater, *OpNDm* optic nerve within dura mater, *POrb* perorbita, *Pclin-ICA* paraclinoidal internal carotid artery (extradural)

not prevent CSF leak during transsphenoidal surgery [3]. When comparing the opening in the center to the size of the stalk, Renn and Rhoton found that the foramen was 5 mm in size in 56% of cases and would not provide a water-tight barrier [3]. In roughly half of the specimens, a diverticulum of arachnoid protruded through the center hole, and this may be a potential cause of post-operative CSF leaks [5].

Cavernous Sinus

Cavernous Sinus Connections Lateral to the sella turcica on either side are the cavernous sinuses (Fig. 10.4). The cavernous segment of the carotid arteries and cranial nerve VI course within these venous blood spaces, whereas cranial nerves III, IV, and the superior division of cranial nerve V are coursing in their respective lateral walls. The cavernous sinuses communicate with each other via variable venous connections that can be found along the edges of the diaphragma and between the two layers of dura surrounding the anterior, inferior, and posterior aspects of the gland itself. These structures are named in relation to their location in reference to the pituitary gland: anterior, inferior, and posterior intercavernous sinuses, respectively. However, the intercavernous connections may occur along any site along the gland. Generally, the anterior intercavernous connection is the largest, but given the variability the connections may range from both being codominant to absent. These are referred to as the circular sinus when both the anterior and posterior connections are intact. Posterior to the dorsum sellae, another large intercavernous connection, the basilar plexus, is found and is often the most consistent of the intercavernous connections. It runs from the dura behind the dorsum

Fig. 10.4 Dural architecture around the pituitary gland. (**a**) exposure following extensive bone removal from planum sphenoidale to clival recess rostro-caudally and over the sella and the parasellar ICAs bilaterally. (**b**) removal of the outer/periosteal dura mater (Reprinted with permission from Zwagerman et al. [17]). (**c**) exposure of inner/meningeal dura mater and opening of the lateral cavernous sinuses. (**d**) removal of the inner/meningeal dura mater. Note the suspension of the inner dura/medial cavernous sinus wall by the carotico-clinoidal ligament system. (**e**) superior view, depicting the extracavernous, extradural clinoidal space antero-medially above the cavernous sinus roof. (**f**) clival dura and microvasculature of the MHT. (**g**) details of the clinoidal space and (**h**) the adhesions between the pituitary capsule and the meningeal dura, hence corresponding to a direct visualization of the medial cavernous sinus wall. (formalin-fixed, silicone injected cadaveric specimen). *LimDm* limbus sphenoidale dura mater, *FlcLig* falciform ligament, *OpNDm* optic nerve within dura mater, *SIS* superior intercavernous sinus, *CavSin* cavernous sinus, *PSLig* Petrosphenoidal (Gruber's) ligament, *CN VI* abducens nerve, *MenDm* meningeal/inner dura mater, *PerDm* periosteal/outer dura mater, *LOCR/OS* lateral opticocarotid recess/optic strut, *Sel* sella turcica, *PCP* posterior clinoid process, *Cliv* clivus, *CapA* capsular arteries (McConnell), *CN II* optic nerve, *OphA* ophthalmic artery, *DDR* distal dural ring, *PDR* proximal dural ring, *Scl-ICA* supraclinoidal internal carotid artery (intradural), *Pclin-ICA* paraclinoidal internal carotid artery (extradural), *Cav-ICA* cavernous internal carotid artery (extradural), *Pcliv-ICA* paraclival internal carotid artery, *OrbFrA* orbitofrontal artery, *Diaph* diaphragma sellae, *Chsm* optic chiasm, *Stlk* pituitary stalk, *PCap* pituitary capsule, *IHA (MHT)* inferior hypophyseal artery of the meningohypophyseal trunk, *ClivBr (MHT)* clival branches of the meningohypophyseal trunk, *ClivDm* clival dura mater, *PcomA* posterior communicating artery, *PIS* posterior intercavernous sinus, *SHA* superior hypophyseal artery, *ClinSp* clinoidal space, *MenCapAd* meningo-capsular adhesions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LimDm
FlcLig
OpNDm
SIS
CavSin
(anterior wall)
PSLig
CN VI
B
MenDm
PerDm
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LOCR/
OS
CapA
Sel (floor)
PCP
Cliv (drilled)
D
Scl-ICA
CN II
OphA
DDR
Pclin-ICA
PDR
Cav-ICA
Pcliv-ICA
E
OrbFrA
Chsm
Stlk
Diaph
PCap
MenDm
CavSin
(medial wall)
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IHA (MHT)
ClivBr (MHT)
ClivDm
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PcomA
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PIS
ClinSp
PDR
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MenCapAd
ClinSp
CavSin
(medial wall)
PCap

sellae to the clival dura. During transsphenoidal surgery robust venous bleeding from these connections can often be controlled with infusion of expansible thrombogenic materials without clinical consequence.

Cavernous Internal Carotid Artery (ICA) To understand cavernous sinus anatomy, the parasellar ICA is essential when using a transsphenoidal approach. The parasellar ICA is divided into two segments: cavernous and paraclinoidal. The cavernous ICA can be subdivided further from proximal to distal: short vertical segment, which is a continuation of paraclival ICA, horizontal segment, and the anterior genu. The posterior genu is located between the short vertical and horizontal subsegments. The *paraclinoidal ICA* is a continuation of the anterior genu as it emerges from within the cavernous sinus. It is located within the clinoidal space at the roof of the cavernous sinus and is limited by the proximal (cavernous roof) and distal dural rings. It is bounded superolaterally by the optic strut. The medial opticocarotid recess at the lateral aspect of the tuberculum is located medial to the paraclinoidal-supraclinoidal ICA transition [6, 7]. The middle clinoid process (Fig. 10.3e) is a variable osseous prominence that extends from the lateral aspect of the sella toward the apex of the anterior clinoid process. Occasionally it can be so prominently developed that it merges with the anterior clinoid process to form a carotico-clinoidal ring, thereby completely encasing the ICA (Fig. 10.3f). Removal of the middle clinoid improves access to the parasellar region; when a carotico-clinoidal ring is encountered it is best to maximally reduce the middle clinoid without fracturing the ring and risk injury to the encased ICA. When present, the middle clinoid process marks the transition between the paraclinoidal and cavernous ICA.

The cavernous sinus has been traditionally described via lateral and superior approaches leading to the development of the surgical triangles of the skull base. With the increasing acceptance of the transsphenoidal route to the cavernous sinus, a revision of the previously described classifications of the cavernous sinus may be helpful for surgical planning. Here we will describe the medial wall and roof of the cavernous sinus, and the venous compartments that are surgically relevant (Fig. 10.5).

Fig. 10.5 (continued) opened to demonstrate the cisternal space and the entry of the cranial nerves III–VI into the cavernous sinus. (**d**) Superior compartment behind the anterior genu of the cavernous ICA, containing the oculomotor and trochlear nerves. (**e**) Posterior compartment, bearing the meningohypophyseal trunk and the gulfar segment of the abducens nerve. (**f**) Inferior compartment, containing the distal abducens nerve and the sympathetic plexus of the ICA. (**g**, **h**) Lateral compartment, bearing all cranial nerves of the cavernous sinus and branches of the inferolateral trunk. For visualization, the ICA has been retracted medially in **h**. (**a**–**h**: formalin-fixed, silicone injected cadaveric specimen). *CN III* oculomotor nerve, *CN IV* trochlear nerve, *CN V1* ophthalmic division of trigeminal nerve, *CN V2* maxillary division of trigeminal nerve, *CN V3* mandibular division of trigeminal nerve, *CN VI* abducens nerve, *Pcliv-ICA* paraclival internal carotid artery, *Symp* sympathetic plexus of the ICA, *VidN* vidian nerve, *PP* posterior pituitary/neurohypophysis, *PcomA* posterior communicating artery, *BA* basilar artery, *PCA* posterior cerebral artery, *SCA* superior cerebellar artery, *PCP* posterior clinoid process, *DorSel* dorsum sellae, *ClivDm* clival dura mater, *IClLig* interclinoidal ligament, *Cav-ICA* cavernous internal carotid artery (extradural), *ClivBr (MHT)* clival branches of the meningohypophyseal trunk, *MPetrApx* medial petrous apex, *IHA (MHT)* inferior hypophyseal artery of the meningohypophyseal trunk, *ILT* inferolateral trunk, *CN II* optic nerve, *DDR* distal dural ring, *PDR* proximal dural ring, *LOCR/OS* lateral opticocarotid recess/optic strut, *OphA* ophthalmic artery, *MS* maxillary strut

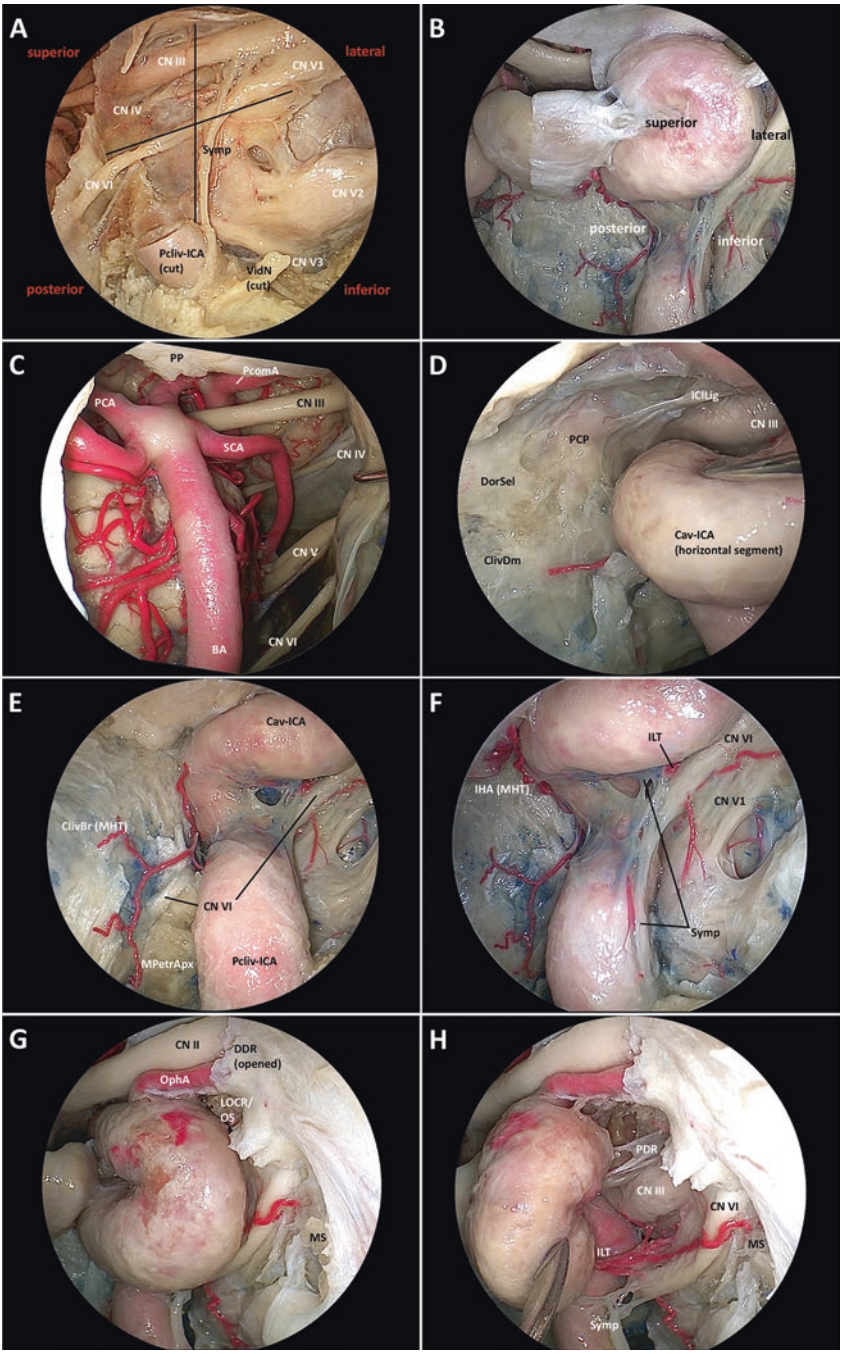


Fig. 10.5 Endoscopic cavernous sinus compartments. From the endonasal endoscopic perspective the cavernous sinus can be subdivided into four distinct compartments (the figure series shows the left side). (**a**) the ICA has been removed to illustrate this concept and to show the structures contained within the cavernous sinus (Reprinted with permission from Zwagerman et al. [17]). (**b**) the ICA is preventing direct access to neurovascular structures. (**c**) the clival dura has been

Medial Wall Surrounding the anterior, inferior, and posterior aspects of the pituitary gland there are two layers of dura mater: an outer periosteal layer and an inner meningeal layer. The periosteal dura extends laterally to form the anterior wall of the cavernous sinus, while the meningeal layer remains attached to the pituitary gland to form the medial wall [8]. Therefore, both the anterior and medial walls of the cavernous sinus consist of a single layer of dura. Superiorly, the medial wall of the cavernous sinus is attached via the carotico-clinoidal ligament. This ligament arises within the dura of the middle clinoid and attaches to the carotid artery and anterior clinoid process. Consisting of multiple thin bands, this ligament forms the medial aspect of the proximal dural ring and continues posteriorly with the interclinoidal ligament at the point where the medial wall and roof of the cavernous sinus meet. Many adenomas are attached to the medial wall, and its complete removal is required for complete tumor resection. In order to do this safely, detachment of the medial wall requires incision of the carotico-clinoidal ligament medial to the carotid artery.

Roof The roof of the pituitary fossa, diaphragma, is composed of a single dural layer that extends laterally to wrap around the paraclinoidal carotid artery and form the distal dural ring. This dura then continues posteriorly as the oculomotor triangle dura. The cavernous sinus roof has both an anterior and a posterior portion. The ventral surface of the paraclinoidal ICA forms the anterior portion, which corresponds to the ventral aspect of the clinoidal triangle. The dura of the oculomotor triangle forms the posterior portion of the roof. The interclinoidal ligament, a firm dural band that connects the anterior and posterior clinoid processes, runs in between the clinoidal and oculomotor triangles. The interclinoidal ligament also separates the medial sellar diaphragm from the lateral oculomotor triangle. The roof of the cavernous sinus is therefore formed by two dural layers: the outer one is a continuation of the sellar diaphragm and the inner one, discontinued, is the interclinoidal ligament. Here it is important to note that a potential space, the clinoidal space, is formed between both layers. This explains the communication between the cavernous sinus and clinoidal space as well as between the sellar and clinoidal space. The interclinoidal ligament continues laterally as the carotid-oculomotor membrane, which completes the proximal dural ring.

Superior Compartment This compartment is located above the horizontal cavernous ICA and behind the posterior surface of the anterior genu. Superiorly and laterally it is bound by the roof of the cavernous sinus or more specifically: medially by the dura of the diaphragm, anterolaterally by the ventral surface of the paraclinoidal ICA, and posterolaterally by the dura of the oculomotor triangle.

The surgical structures of this compartment include the oculomotor nerve, which runs in the lateral wall of this compartment between two layers of dura; this segment of the nerve can be identified as the interdural segment [15]. The nerve penetrates the inner layer of dura on the superior aspect of the lateral wall of the cavernous sinus just lateral to the anterior genu of the cavernous ICA, once it enters the clinoidal triangle. One of the important landmarks identified within the superior compartment is the interclinoidal ligament. This ligament is located lateral and posterior to the paraclinoidal ICA and medial and anterior to the oculomotor nerve.

In order to surgically access the superior compartment, the bone that overlies the anterior wall of the cavernous sinus and paraclinoidal ICA must be completely removed. This permits lateral displacement of the ICA for surgical dissection. Access to the superior compartment is performed though the medial wall of the cavernous sinus. Tumors invading this compartment typically destroy the medial wall and grant access more readily. Mobilization of the carotid artery from medial to lateral grants further access. Angled endoscopes are required to maximize visualization. The interdural segment of the oculomotor nerve is protected as long as the lesion does not invade and extend beyond the lateral wall of the cavernous sinus. The most vulnerable segment of the oculomotor nerve is at the point where it penetrates the lateral wall of the cavernous sinus just lateral to the anterior genu of the ICA. The interclinoidal ligament, located just lateral to the oculomotor nerve, is the landmark structure in this compartment and for identification of the nerve.

Posterior Compartment The anterior boundary of this compartment is the posterior wall of the short vertical cavernous ICA and the posterior boundary is the lateral petro-clival dura composing the posterior wall of the cavernous sinus. The border between the posterior compartment and the superior compartment is marked by the transition between the short vertical and horizontal subsegments of the cavernous ICA.

Arising from the posterior aspect of the posterior genu of the cavernous ICA is the meningohypophyseal trunk. This trunk branches and gives off the inferior hypophyseal and the dorsal meningeal artery. The inferior hypophyseal artery travels medially and anteriorly toward the dura of the sellar, whereas the dorsal meningeal artery travels posteriorly and infero-medially toward the dura of the dorsum sella. The gulfar segment of the abducens nerve is found in the inferior portion of this compartment as it passes through Dorello's canal behind the ICA. This segment is located just above the medial aspect of the petrous apex and is bounded posteriorly by the petrosphenoidal or Gruber's ligament [9]. This segment of the abducens nerve is located at the confluence of the inferior and superior petrosal sinuses as they merge with the basilar plexus to discharge into the cavernous sinus. Here, the nerve is void of its surrounding protecting dural layer [9].

Surgical access to the posterior compartment begins with complete bone removal of the anterior face of the cavernous sinus and pituitary gland. This has to be extended inferiorly to expose the entry point of the carotid artery into the cavernous sinus marking the transition between the paraclival ICA and the cavernous ICA. This is best performed from a medial to lateral technique to expose the sellar floor and follow this laterally until the transition to the cavernous sinus and the ICA entrance point is visualized. To gain access to the posterior compartment, the short vertical segment of the ICA after it enters the cavernous sinus must be mobilized laterally which often necessitates the coagulation and ligation of the inferior hypophyseal artery which tethers the ICA to the dura. This has been done safely and without consequence and prevents possible avulsion during the surgery [8]. The landmark for the abducens nerve in the posterior compartment is the short vertical ICA. Electrostimulation will confirm the presence of the abducens nerve at the floor

of this compartment and just behind the ICA. This area may produce brisk venous bleeding from the inferior petrosal sinus and management requires caution as coagulation and even packing may result in nerve damage.

Inferior Compartment This compartment is bound superiorly by the inferior surface of the horizontal ICA and anteriorly by the anterior wall of the cavernous sinus. The posterior border is the anterior surface of the short vertical ICA subsegment.

This compartment houses the sympathetic plexus that travels along the carotid from the short vertical segment to the horizontal segment. The abducens nerve segment in the distal cavernous sinus is located lateral and inferior to the horizontal segment of the ICA marking the transition point between the inferior and lateral cavernous compartments. Located lateral to the sympathetic plexus, the abducens nerve travels in a horizontal direction whereas the sympathetic plexus travels a more oblique path.

A supravidian transpterygoid approach grants access to [10–12] the lateral recess of the sphenoid sinus and permits wide opening for full access to the lateral wall of the sphenoid sinus. To access this compartment, the bone covering the anterior face of the cavernous sinus must be removed. This is further extended by removing the bone up to the dural fold at the transition between the parasellar region and the middle cranial fossa, which corresponds to the petrolingual ligament/process inferiorly. This facilitates the opening of the dura inferior to the horizontal segment of the carotid to access the inferior cavernous compartment. This compartment may be filled with tumor, which facilitates opening this compartment with the horizontal segment being moved superiorly. A key tool for this step is an intraoperative doppler probe to identify the cavernous ICA as it transitions from the horizontal carotid to the anterior genu. The first landmark during inferior compartment dissection is the sympathetic nervous plexus, located medially to the abducens nerve. During dissection, electrical stimulation will help to identify the abducens nerve as it travels parallel to the horizontal carotid. Often it is located more lateral and inferior than the horizontal carotid itself.

Lateral Compartment The medial boundary of this compartment consists of the lateral horizontal and anterior genu segments of the cavernous carotid. The superior surface is bound by the proximal dural ring at the inferior surface of the optic strut. The inferior boundary is formed by the maxillary strut, which separates the foramen rotundum from the superior orbital fissure. The anterior/lateral boundary lies at the plane of the optic and maxillary struts binding the superior orbital fissure where cranial nerves III, IV, and VI exit the cavernous sinus.

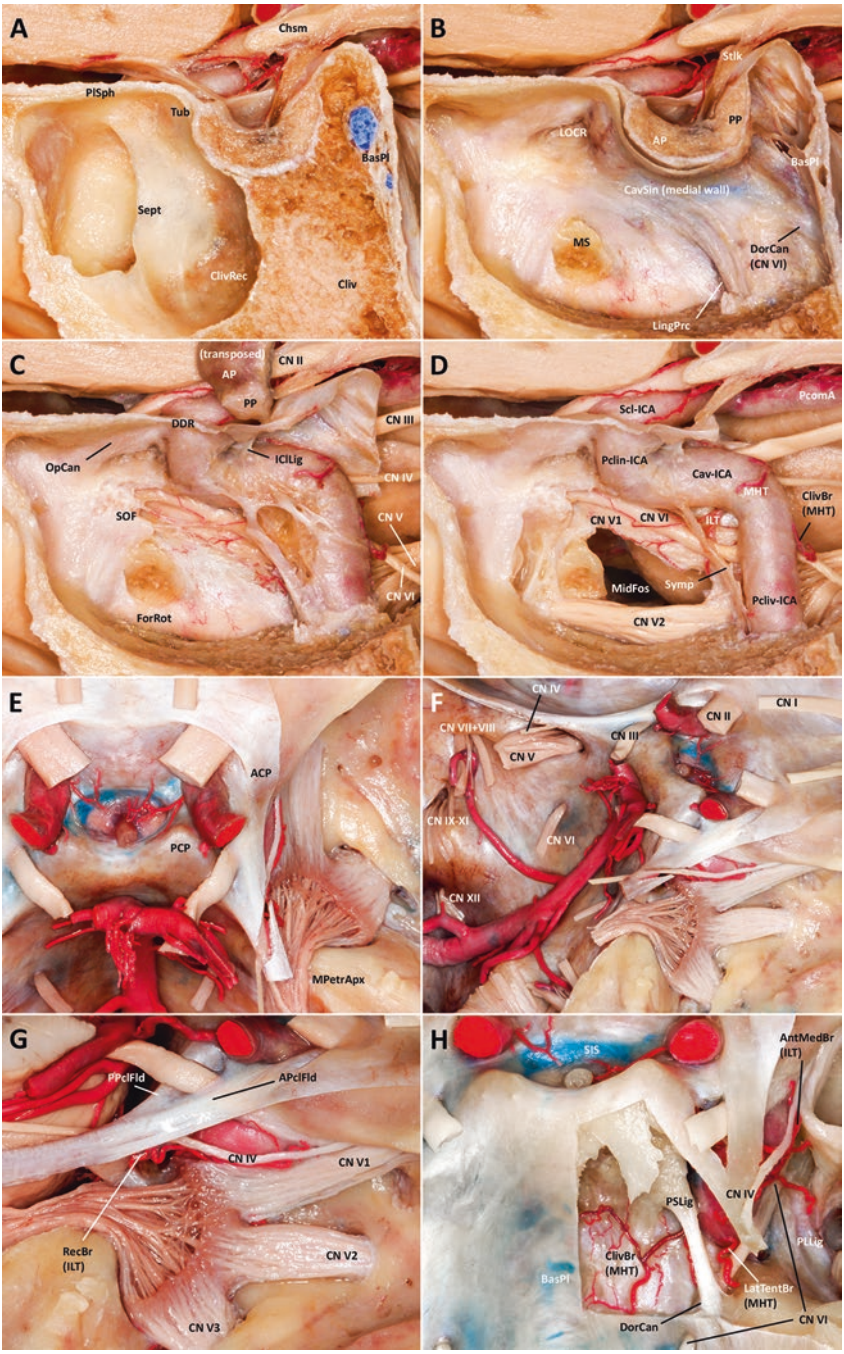
Located in the lateral wall of the cavernous sinus, cranial nerves III, IV, and the first division of cranial nerve V pass through the cavernous sinus. The distal segment of the abducens nerve is located at the transition between inferior and lateral compartments. A branch of the internal carotid artery, the inferolateral trunk, arises from the inferior aspect of the horizontal cavernous carotid and runs medial to lateral supplying the lateral wall of the cavernous sinus, usually passing between cranial nerves V1 and VI.

The risk of cranial nerve injury when accessing this compartment is high. To access this compartment, the bone covering the anterior genu, paraclinoidal carotid, and the cavernous sinus up to the superior orbital fissure must be removed. The optic strut serves as the superior boundary, whereas the maxillary strut serves as the inferior boundary. The anterior wall of the cavernous sinus is opened from an inferior to superior direction directly in front of the anterior genu of the ICA. The use of intraoperative doppler of the ICA can be crucial at this point for exact localization of the artery. The surgical corridor is between the horizontal and anterior genu of the carotid as well as the cranial nerves laterally. Often, tumors in this area expand the distance between the carotid and the lateral wall making this dissection easier. However, the abducens nerve may be embedded within tumor here and is unprotected leading to increased risk of injury. This corridor may be expanded by mobilizing the carotid in a lateral to medial direction. This is performed by cutting the proximal dural ring, which extends from the paraclinoidal ICA and the lower aspect of the optic strut. While dissecting in the lateral compartment, it is important to carefully identify, coagulate, and cut the inferolateral trunk and its branches coming off the carotid to prevent inadvertent injury or avulsion. The use of electrical stimulation will help to identify the cranial nerves as they transverse through the lateral compartment permitting safe dissection; however, our experience has shown that often tumors that invade the lateral compartment may also invade the lateral wall preventing complete resection.

Suprasellar Region

The space formed by the opening of the tentorium is called the incisura. The anterior incisural space is located directly in front of the brainstem and is commonly encountered during dissection for suprasellar and retrosellar lesions. The middle incisural space is located lateral to the midbrain and the posterior incisural space is located posterior to the midbrain. The part of the anterior incisura located below the optic chiasm, infrachiasmatic space, is bounded posteriorly by Lillequist membrane and laterally by the supraclinoidal ICA. Laterally, the anterior incisura opens to the Sylvian fissure just below the anterior perforated substance. The pituitary stalk transverses the anterior tentorial incisura in a cranial-caudal direction to enter the sella. The part of the anterior incisura above the optic chiasm, suprachiasmatic space, is limited superiorly by the rostrum of the corpus callosum, laterally by the medial surface of the frontal lobes, and posteriorly by the lamina terminalis (Fig. 10.6). The suprasellar cistern communicates with the suprachiasmatic cistern via the optic-carotid cisterns lateral to the optic nerves and chiasm.

Cranial Nerves The olfactory tracts travel posteriorly from the cribriform plate and divide at the posterior end of the olfactory sulcus into medial and lateral olfactory striae, which define the anterior border of the anterior perforated substance. The optic nerves exit the optic canals medial to the anterior clinoid to join at the optic chiasm. As each nerve exits the canal, they are covered superiorly by a thin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CavSin (medial wall)
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DorCan (CN VI)
LingPrc
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(transposed) AP
CN II
PP
DDR
CN III
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Scl-ICA
Pclin-ICA
Cav-ICA
MHT
ClivBr (MHT)
CN V1
CN VI
ILT
MidFos
Symp
Pcliv-ICA
CN V2
E
ACP
PCP
MPetrApx
F
CN IV
CN I
CN II
CN VII+VIII
CN III
CN V
CN IX-XI
CN VI
CN XII
G
PPclFld
APclFld
CN IV
CN V1
RecBr (ILT)
CN V2
CN V3
H
SIS
AntMedBr (ILT)
PSLig
CN IV
PLLig
ClivBr (MHT)
BasPl
LatTentBr (MHT)
DorCan
CN VI

layer of dura known as the falciform ligament [3], which extends from the medial aspect of the anterior clinoid to the limbus of the sphenoid. The optic tracts emerge from the optic chiasm and travel in a posterior-lateral direction around the cerebral peduncles to enter the middle incisural space.

When approaching the optic nerves from a transsphenoidal route, they are located above the opticocarotid recess or optic strut. The length of the optic canal is equal to the length of the optic strut [13]. When decompressing the nerve, care must be taken to prevent damage by transferred heat, and drilling of the overlying bone requires constant copious irrigation. From the endonasal route, the falciform ligament is best opened in a medial to lateral direction, visualizing the intracranial nerve to minimize the risk of damage to the nerve. Similarly, the dura of the optic nerve is best opened on the superior medial surface to prevent injury to the ophthalmic artery.

The optic chiasm and its relationship with the sella have been previously described in three ways. In 70% of cases the chiasm sits directly over the sella. In 30% of cases the distribution is split between the prefixed position where the chiasm sits over the tuberculum sellae and the postfixed position where the chiasm is located over the dorsum sellae [3].

Fig. 10.6 Microscopic anatomy of the cavernous sinus and skull base (Copyright held by UPMC Center for Cranial Base Surgery). (**a–d**) Stepwise dissection of the medial cavernous sinus wall after mid-sagittal hemisection. (**a**) removal of the mucosa within the sphenoid sinus. (**b**) removal of clival bone including posterior clinoid processes. Note the optic and maxillary struts, landmarks for optic canal, superior orbital fissure and foramen rotundum respectively. (**c**) the pituitary is transposed superiorly for visualization, the dura has been partially opened and removed. (**d**) complete resection of cavernous and middle fossa dura, demonstrating the course of the cranial nerves and microvasculature. (**e**) superior view onto the perisellar region. (**f**) oblique view into the anterior, middle and posterior cranial fossae, demonstrating the dural entry of all 12 cranial nerves. (**g**) detail of the right trigeminal ganglion. (**h**) posterior view, the trigeminal ganglion has been elevated to show the petrolingual ligament and the course of the abducens nerve. (**a–h**: formalin-fixed, silicone injected cadaveric specimen). *PlSph* planum sphenoidale, *Chsm* optic chiasm, *Tub* tuberculum sellae, *Cliv* clivus, *ClivRec* clival recess, *Sept* septations within sphenoid sinus, *BasPl* basilar plexus, *LOCR* lateral opticocarotico recess, *MS* maxillary strut, *CavSin* cavernous sinus, *DorCan* Dorello's canal, *Stlk* pituitary stalk, *LingPrc* lingual process (sphenoid bone), *AP* anterior pituitary/adenohypophysis, *PP* posterior pituitary/neurohypophysis, *OpCan* optic canal, *SOF* superior orbital fissure, *ForRot* foramen rotundum, *DDR* distal dural ring, *IClLig* interclinoidal ligament, *CN II* optic nerve, *CN III* oculomotor nerve, *CN IV* trochlear nerve, *CN V* trigeminal nerve, *CN VI* abducens nerve, *Scl-ICA* supraclinoidal internal carotid artery (intradural), *Pclin-ICA* paraclinoidal internal carotid artery (extradural), *Cav-ICA* cavernous internal carotid artery (extradural), *Pcliv-ICA* paraclival internal carotid artery, *MHT* meningohypophyseal trunk, *ILT* inferolateral trunk, *ClivBr (MHT)* clival branches of the meningohypophyseal trunk, *MidFos* middle cranial fossa, *CN V1* ophthalmic division of trigeminal nerve, *CN V2* maxillary division of trigeminal nerve, *Symp* sympathetic plexus of the ICA, *PcomA* posterior communicating artery, *ACP* anterior clinoid process, *PCP* posterior clinoid process, *MPetrApx* medial petrous apex, *CN I* olfactory nerve, *CN VII* facial nerve, *CN VIII* vestibulocochlear nerve, *CN IX* glossopharyngeal nerve, *CN X* vagal verve, *CN XI* accessory nerve, *CN XII* hypoglossal nerve, *CN V3* mandibular division of trigeminal nerve, *APclFld* anterior petroclinoidal fold, *PPclFld* posterior petroclinoidal fold, *RecBr (ILT)* recurrent branch of the inferolateral trunk, *AntMedBr (ILT)* anteromedial branch of the inferolateral trunk, *LatTentBr (MHT)* lateral tentorial branch of the meningohypophyseal trunk, *PSLig* Petrosphenoidal (Gruber's) ligament, *PLLig* petrolingual ligament, *SIS* superior intercavernous sinus, *BasPl* basal plexus

Vasculature When approaching the suprasellar region, it is critical to understand the relationships between the optic nerves, carotid artery, and anterior clinoid process. Intracranially, the anterior clinoid process is lateral to the optic nerve. As the carotid artery leaves the cavernous sinus and transverses the proximal and distal dural rings it emerges below and medial to the optic nerve. The nerve continues a posterior-medial course to the optic chiasm whereas the carotid travels in a posterior-lateral course to the bifurcation.

The vasculature of the suprasellar region is complex and involves several feeding and anastomotic arteries of both the anterior and posterior circulation. The anterior incisura contains the posterior half of the circle of Willis including the basilar apex and posterior communicating arteries. The anterior communicating arteries lie directly above the optic chiasm. The ophthalmic artery is the first branch off the intracranial ICA and travels along the inferior surface of the optic nerve. The superior hypophyseal arteries supply the pituitary gland, infundibulum, and optic chiasm via several small branches.

As stated earlier, the internal carotid artery reaches the anterior incisural space by traveling along the inferior-medial side of the anterior clinoid. The artery then continues in a superior-posterior-lateral direction to the anterior perforated substance where it bifurcates to form the anterior and middle cerebral arteries. When viewed from a transsphenoidal approach, the artery initially lies on the inferior-medial side of the optic nerve, but once it becomes intradural it translates to a lateral position. The superior hypophyseal artery branches off the carotid artery in the suprasellar space and travels medially to meet its contralateral branch around the infundibulum. Care must be taken when dissecting this area as to not injure perforators which may be supplying the chiasm and optic nerves [14]. The supraclinoidal carotid artery is divided into three segments based on the major branching arteries. The first segment is the ophthalmic segment, which corresponds to the ICA between the ophthalmic artery origin to the origin of the posterior communicating artery. The communicating segment spans from the posterior communicating artery to the origin of the anterior choroidal artery. Finally the choroidal segment contains the ICA from the anterior choroidal artery to the bifurcation [14]. Each segment may contain perforating arteries that supply the optic nerves, optic tracts, and the midbrain itself.

The first branch off the supraclinoidal ICA is the ophthalmic artery. This artery has significant variability as it may arise in the cavernous sinus, intradural or be absent [2, 3]. This artery usually runs along the undersurface of the optic nerve. The second branch off the carotid is often the superior hypophyseal artery that runs medially to join the contralateral superior hypophyseal artery around the infundibulum supplying branches to the optic nerves and chiasm along the way. Care must be taken to not injure these perforating arteries to prevent visual symptoms. The posterior communicating artery arises from the posterior surface of the ICA and courses in a posterior-medial direction under the optic tracts to join the posterior cerebral arteries. Perforating branches from this artery supply deep brain structures including the internal capsule and thalamus. The size of this artery is quite variable, and it

may provide significant blood supply to the posterior cerebral artery or none at all. This artery runs just above the oculomotor nerve [15]. The last branch before the bifurcation is the anterior choroidal artery, which arises from the posterior ICA just distal to the origin of the posterior communicating artery and courses in a posterior-lateral direction between the uncus and the cerebral peduncles under the optic tracts. This branch supplies the basal ganglia as well as the midbrain. The anterior cerebral artery is a terminal branch of the ICA and travels in an anterior-medial direction above the optic nerve toward the interhemispheric fissure. Here, the artery is joined by the contralateral corresponding anterior cerebral artery and anastomoses via the anterior communicating artery. The junction of these arteries is most often found directly above the chiasm [3]. The recurrent artery of Heubner is usually seen in this location as well. This artery may arise from the proximal anterior cerebral artery, the anterior communicating artery, or the distal anterior cerebral artery. It courses laterally above the ICA bifurcation to supply the anterior perforated substance [16].

Retrosellar Region: Interpeduncular Cistern

In the posterior aspect of the anterior incisura, behind the dorsum sellae, sits the interpeduncular cistern, which communicates anteriorly with the infrachiasmatic space and suprasellar cistern. These two cisterns are separated from each other by the membrane of Lillequist. This membrane is composed of arachnoid and extends from the dorsum sellae to the anterior surface of the mammillary bodies. The interpeduncular cistern is bounded posteriorly by the cerebral peduncles and laterally by the uncus of the temporal lobe.

Vasculature The basilar artery is formed from the paired vertebral arteries near the ponto-medullary junction and travels along the surface to the midbrain where it terminates into the paired posterior cerebral arteries. Along its course, several perforating arteries supply the brainstem and cranial nerves in the near proximity. During retrosellar and transclival approaches, these can be seen along with the paired anterior inferior cerebellar arteries. The paired superior cerebellar arteries arise just proximal to the terminal bifurcation of the basilar artery. The oculomotor nerve travels between the posterior cerebral and superior cerebellar arteries.

Cranial Nerves The oculomotor nerve extends from the midbrain to the cavernous sinus as it runs in the lateral aspect of retrosellar space. This is identified from its origin as it runs between the posterior cerebral artery and the superior cerebellar artery. The trochlear nerve runs in the tentorium edge around the incisura to enter the cavernous sinus below the level of the oculomotor nerve. The trigeminal nerve can be seen arising laterally from the superior aspect of the pons as it enters Meckel's cave. The abduces nerve arises on the ventral surface of the pons and has a short cisternal segment before it enters a sleeve of dura (Dorello's canal).

Conclusion

The anatomy of the sellar region is complex and serves as the crossroads for many of the arteries and cranial nerves entering and leaving the skull base. Detailed knowledge of this region is paramount for safe surgical access and treatment of many central skull base lesions.

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11 Combined Hybrid Microscopic and Endoscopic Transsphenoidal Surgery: Anatomy, Instrumentation, and Technique

David S. Baskin and Robert A. Scranton

Introduction

In 1906, Sir Victor HorseIy described his 1889 pituitary surgery using a transcranial approach [1], and in 1907 Hermann Schloffer, an otorhinolaryngologist, performed the first transsphenoidal pituitary operation approaching through a lateral rhinotomy. Unfortunately, the patient only survived for 2 months [2–4]. Since the advent of these approaches, surgical techniques for the management of pituitary pathology have undergone significant evolution. The early 1900s saw many variations of surgical technique including transnasal, transethmoidal, and infranasal approaches to the sella pioneered by Arnold Chiari, Allen Kanavel, Albert Halstead, Harvey Cushing, and Oskar Hirsch [3–6]. Hirsch's technique was remarkably similar to the more current technique of a submucosal transseptal approach, with a submucosal dissection along the septum to approach the sphenoid sinus [7]. Harvey Cushing's sublabial approach has endured the test of time; however, he later favored the transcranial approach citing better visual outcomes and easier reoperation [8]. Many surgeons

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Electronic supplementary material: Supplementary material is available in the online version of this chapter at 10.1007/978-3-319-56691-7_11. Videos can also be accessed at http://www.springerimages.com/videos/978-3-319-56689-4.

D.S. Baskin, MD, FACS, FAANS (✉)
Professor, Vice Chair, and Program Director, Department of Neurosurgery, Houston Methodist Neurological Institute, Houston, 77030 TX, USA

Director, Kenneth R. Peak Brain and Pituitary Tumor Treatment Center, Department of Neurosurgery, Houston Methodist Neurological Institute, Houston, 77030 TX, USA
e-mail: dbaskin@houstonmethodist.org

R.A. Scranton, MD
Kenneth R. Peak Brain and Pituitary Tumor Treatment Center and Department of Neurosurgery, Houston Methodist Neurological Institute, Houston, 77030 TX, USA

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_11

followed his lead [9, 10]. The sublabial approach lost favor but was kept alive by Norman Dott who passed it on to Gerard Guiot, a French neurosurgeon [4]. Guiot's major contributions included the use of intraoperative fluoroscopy which allowed for real-time feedback on instrument position and tumor removal, as well as being the first to report the use of an endoscope. Jules Hardy learned the transsphenoidal technique while a fellow with Guiot and applied the operating microscope to the procedure to solve the problems of inadequate lighting and magnification [3, 5, 11]. These historic moments set the stage for the modern transnasal endoscopic approach to the pituitary gland [12].

The past decade has seen vast improvements in instrumentation including the lighting and resolution of endoscopes, the development of CCD chip cameras, and the development of angled endoscopes. These advances have stimulated shifts in practice patterns from microsurgical to endoscope-assisted microsurgery and more recently purely endoscopic transnasal approaches. Proponents of each method list limitations of the competing technique as evidence for the superiority of one method over the other. Champions of a purely microsurgical approach cite the three-dimensional view afforded by the microscope, the ability for bimanual operation without the need for a second surgeon or machine to hold the endoscope, and the increased space for operating instruments when a sublabial approach is utilized. The purely microsurgical approach avoids the purported "swordfighting" problem, where instruments touch, collide, and limit free motion. Conversely, advocates of a pure endoscopic approach rebut citing the wider field of view gained with the endoscope to visualize much more anatomy, use of angled scopes to see around corners and the ability to navigate around a fixed space. We believe that the on-going debate is analogous to the "clip-versus-coil" debate for intracranial aneurysm treatment, where there is no clear winner, but rather a time and place for each technique. The senior author (DSB) has utilized a hybrid approach in over 3500 patients. His hybrid approach is beyond endoscope-assisted microsurgery – both tools are on equal footing and are almost always both used during surgery at particular points in time or to address specific surgical issues. Both surgical approaches are utilized to achieve optimal outcome, and it is the senior author's belief that the debate emphasizes incorrect issues. The modern-day pituitary surgeon should feel equally at ease with both techniques and use both freely.

Case Preparation

Periprocedural Communication and Safety

Transsphenoidal removal of pituitary tumors is a rewarding operation with good patient outcomes; however, the innumerable details are paramount in order to avoid disaster. Standardized checklists have been created for a number of procedures and complex clinical situations to ensure a smooth operation and minimize confusion. Transsphenoidal operations involve many steps with a large amount of specialized equipment and lend itself well to this practice. Some checklists have been published and we have been published and we encourage others to develop their own

and make its use standard [13, 14]. Ideally the operating room and its equipment should be set up and inspected prior to intubating the patient; otherwise, it must be accomplished before beginning the procedure. Broken or missing unique and critical instruments can create problematic scenarios.

Clear communication is paramount with all operating room personnel including the anesthesiologist, circulating nurse, and scrub nurse. The need for specialized, nonstandard equipment, such as a lumbar drain setup or micro Doppler, should be communicated to avoid delays. The surgeon should be present from the point the patient enters the room through extubation to monitor for any potentially serious complications. Patients with significant optic nerve compression can be susceptible to further nerve damage with periods of hypotension such as during induction or while the anesthesiologist is placing additional lines. The operative plan such as cavernous sinus dissection should be discussed prior to surgery. In this case, a precordial Doppler or central venous catheter is recommended to monitor or treat a potential venous air embolism.

OR Setup

The operating room for the hybrid approach is set up for a right-sided craniotomy, with anesthesia positioned on the patient's left and the table in C-arm position (Fig. 11.1). The surgeon, assistant, scrub nurse, and back table are positioned on the patient's right. We use a room specially designed for endoscopic procedures with ceiling-mounted screens and a tower with endoscopic equipment (light source, recording unit, and endoscope irrigation system), cautery sources, and drill console positioned at the patient's feet. For quick access, the microscope is balanced and draped in the corner opposite anesthesia, closest to the sterile core. Monitors are positioned at the patient's head on a tower for displaying the patient's preoperative MRI for reference, fluoroscope output, and the endoscope view. We route the fluoroscope view to the same screen as the endoscope as a picture-in-picture, so the surgeon can focus on the same screen for comfort. The robotic Mitaka Point Setter® (Mitaka USA, Park City, Utah) is attached to the operating room table accessory rail on the patient's right side at approximately shoulder level to hold the endoscope. We routinely use intraoperative fluoroscopy for navigation in our procedures and position it at the head of the bed to acquire a lateral skull view magnified on the sella. Stereotactic navigation is also utilized in complex cases.

Patient Positioning and Preparation

The operating table is in C-arm position with the cranial fixation attachment in place. The patient is in a modified semi-sitting position in our approach with the head elevated above the level of the heart. The patient is supine with the back flexed approximately 45° and the hips and knees in slight flexion with a lap belt placed so as to prevent the patient from sliding. The left arm rests on an airplane-style arm board at the level of the heart with an arterial line. Foam padding is used on the

Fig. 11.1 Operating room setup for a hybrid transsphenoidal procedure: The room is setup for a right-sided craniotomy with anesthesia on the left and surgeon, assistant, scrub nurse, and instruments on the right. A C-arm is positioned for intraoperative fluoroscopy, the endoscope is affixed to the table with a Mitaka arm and the microscope is draped and ready to be used when required. A semi-sitting position is utilized for several reasons. First the position is much more comfortable for the surgeon rather than leaning over the patient. Even more important, though, is that the semi-sitting patient allows blood to settle in the bottom of the field, minimizing the obscuring effects of a small amount of venous oozing

volar surface of the right arm that wraps dorsal to cover the elbow and is secured in flexion at the elbow across the body to the contralateral shoulder. The left side of the body and legs are covered with a forced-air warming blanket, and the right lower quadrant of the abdomen is exposed for harvesting a fat graft. Inherent to this position is the possibility of venous air embolism. While one would expect that there is an increased risk of venous air embolism in the sitting position, the senior author (DSB) has never experienced this in over 4300 transsphenoidal procedures, despite frequent entry into the cavernous sinus in patients with large tumors. The cavernous sinus has many valves and baffles that inhibit transmission of air into it preventing venous air embolism; therefore, a central line is not routinely placed. A precordial Doppler is used in this position which is audible to the surgeon and anesthesiologist. A Foley catheter is also placed for the procedure, but may be discontinued prior to emergence from anesthesia. An arterial line is used for accurate blood pressure monitoring in the left radial artery (opposite the surgeon) on a lateral arm board, and is

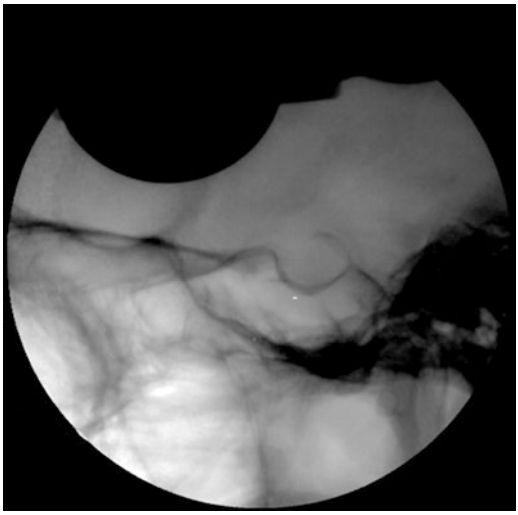

Fig. 11.2 Lateral skull fluoroscopy focused on the sella turcica. If one uses the C-arm, it is important to align the planum sphenoidale and the sphenoid wings properly to prevent parallax errors

zeroed at the level of the head, to ensure adequate cerebral perfusion. This is critically important in patients with significant optic apparatus compression where a relative hypotension may lead to optic nerve ischemia. The endotracheal tube is secured to the left, away from the surgeon, and the cuff is inflated so that air does not reflux into the nasal sinuses which can produce fogging of the endoscope lens.

Once the patient's body is secured, cranial fixation pins are placed in a position so as not to obstruct the fluoroscopy (Fig. 11.2). Although not routinely performed, stereotactic neural navigation is also utilized. Errors in registration are significant and can produce misleading information. Alternatively, a radiolucent holder can be used. The head is positioned slightly ventral in a sniffing position with slight neck extension and the head is rotated to the right to present the nostrils at a comfortable angle to the surgeon (Fig. 11.3). Proper alignment is important. If the surgeon places his or her thumbs at the level of the nostrils, and the index fingers on the most anterior aspect of the ear cartilage on both sides, this is the angle of entry into the sella.

This approach is usually uni-nostril; therefore, laterality is based on patient and tumor characteristics. The position of the tumor determines which nostril to approach through, as long as there are no anatomic contraindications in the anterior nasal passages. The most direct line of sight is achieved by approaching tumors that are eccentric to the left of midline through the right nostril and vice versa. This allows the surgeon to use an approach angle that maximizes visualization and maneuverability.

Saline moistened 2-inch cotton packing is placed in the oropharynx as a throat pack to catch any mucus, blood, or irrigation that may drain from the sinuses during the operation and decreases the risk of aspiration and postoperative emesis. It is important to truly pack the throat and not the mouth, so that a barrier to blood traveling down the esophagus is created.

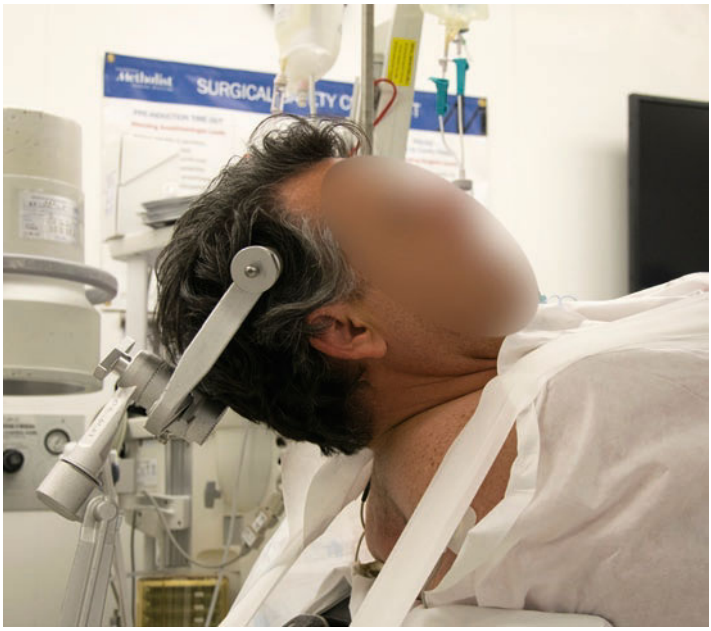

Fig. 11.3 Photograph demonstrating the positioning of Mayfield cranial pins and Mitaka arm so that an unobstructed lateral view of the sella can be obtained with intraoperative fluoroscopy. It is crucial to remain fairly superior with the points of fixation to avoid visualization of the pins in the lateral fluoroscopy

Oxymetazoline 0.05% spray, an alpha agonist, is administered in each nostril followed by cotton pledgets soaked in 4% cocaine solution; both act as potent vasoconstrictors. The pledgets are left in the nasal cavity throughout the prepping and removed at the start of the transnasal portion of the operation. To avoid corneal damage, the eyes are covered with an artificial tear gel and transparent film dressing before nasal cocaine application. Cocaine is classified as pregnancy category C and is avoided in pregnant patients. In addition, caution is advised in patients with a history of drug abuse and cardiovascular disease. Alternatively, the nasal mucosa can be injected with 1% lidocaine with epinephrine 1 : 100,000 dilution. The external nose and right lower quadrant of the abdomen are then prepped and draped in standard fashion.

Lumbar Drain

The patient's imaging is studied with attention to the presence and degree of suprasellar tumor extension. If needed, a lumbar drain is placed after intubation prior to positioning. The lumbar drain is used to aid in the resection of the suprasellar component of large adenomas, and is particularly useful for those tumors that are soft in consistency. Following standard drain placement, a sterile system is

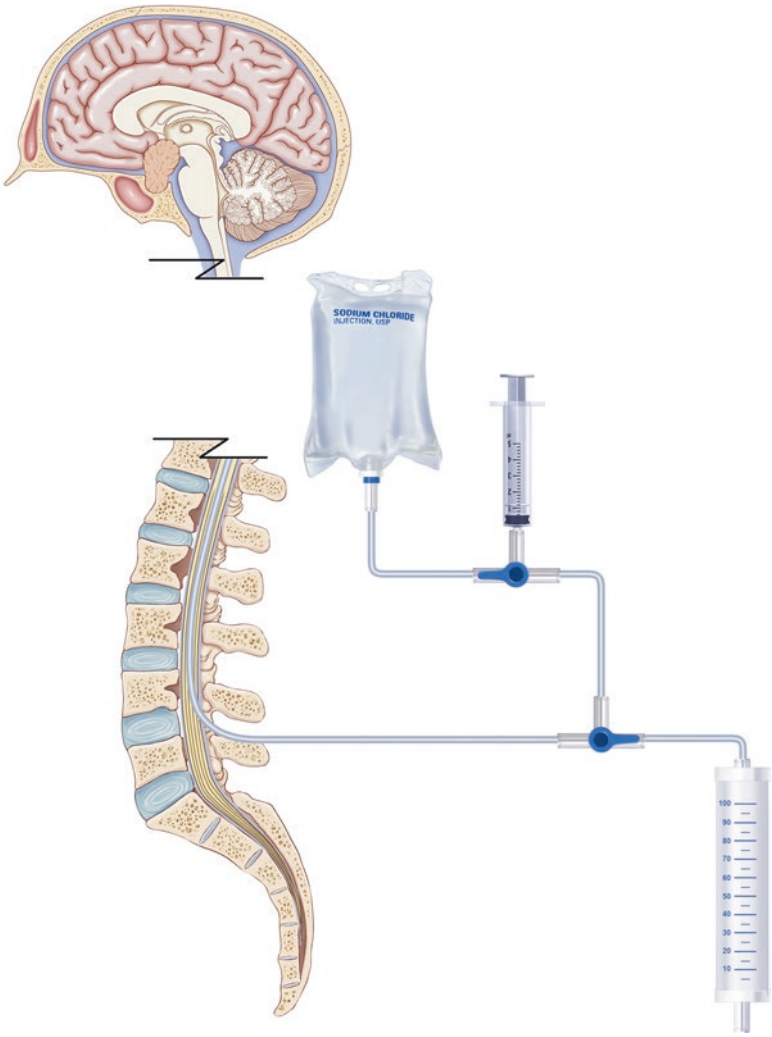

Fig. 11.4 Artist's depiction of lumbar drain setup. A lumbar drain is placed and connected to a series of sterile tubing and three-way stop-cocks creating a sterile system for injecting preservative-free saline or removing CSF. This technique aids in tumor resection. The anesthesiologist can either inject into the patient to increase intracranial pressure and push the tumor and suprasellar cistern downward, or withdraw fluid from the patient to relax pressure and encourage upward migration of the suprasellar cistern to aid visualization of the posterior sellar region

constructed (Fig. 11.4) consisting of a 250-mL bag of injectable saline connected to a three-way stopcock with a 20-mL Luer lock syringe. The system continues to connect to an additional three-way stopcock, intercepting the proximal and distal portion of the drain line. The drain line stopcock is taped to be "off" to the collection system so injectable saline is directed toward the patient during the procedure. This

arrangement allows sterile fluid to be introduced or removed from the intrathecal space, increasing or decreasing intracranial pressure, respectively. Adenomas that are soft can often be pushed down from the suprasellar position presenting itself to the surgeon in the sella when intracranial pressure is increased. This maneuver is expedient but must be performed with careful communication with the anesthesiologist. The intrasellar component of the tumor is resected prior to injecting the saline to make room for the descent of the remainder of the tumor. It is also recommended to relieve as much optic nerve compression as possible through manual tumor removal prior to injecting saline. If the tumor is firm and/or fibrous, the maneuver can still be of value. In order to avoid damage to vessels attached to the tumor surface, great care must be taken to not place undue traction force on the tumor as it descends. The maneuver is to gently peel the tumor away from the pseudocapsule and the arachnoid. This maneuver allows the tumor to come into view, descending into the sella and occasionally even the sphenoid sinus.

In cases where the tumor will not descend, the endoscope is very valuable. In this setting, the endoscope allows the surgeon to look upwards and free up fibrous bands or other structures that may be preventing the tumor from descending.

Contraindications to this maneuver include firm tumors that do not descend after injection, and contraindications to lumbar drain placement such as arachnoiditis. Intraoperative CSF leak is not a contraindication but caution is advised as increasing intracranial pressure may exacerbate the leak. Also, once there is a leak, it is difficult to increase intracranial pressure which is what encourages downward descent of the tumor. The increased intracranial pressure can cause potential complications, which include difficulties with lumbar drain displacement, optic apparatus damage, and CSF leak. We have never seen any major complications with this technique in our experience. If successful, the surgeon reduces the need to dissect around critical structures in the suprasellar compartment, where even with an angled endoscope, visualization can be difficult.

Surgical Technique

A standardized time-out checklist procedure is used before beginning the procedure. Unless there is a clear indication, we minimize disruption of the native sinus anatomy as much as possible. To this end, we do not routinely resect the middle turbinate or harvest a nasal-septal flap. The abdominal portion of the procedure is rapid and uses comparatively few instruments. Completing this portion avoids cross contamination between the surgical trays, and the instruments can be passed off the field at the beginning. A 3 cm × 3 cm × 3 cm fat graft is usually sufficient for all operations, but the size should be determined based on review of the imaging prior to surgery. Ideally, the graft is harvested as one piece or with as few pieces as is feasible. This makes the graft easier to work with later in the procedure and maintains the microvascular structure within the graft. Multiple small pieces may result in more graft necrosis and increased nasal drainage postoperatively.

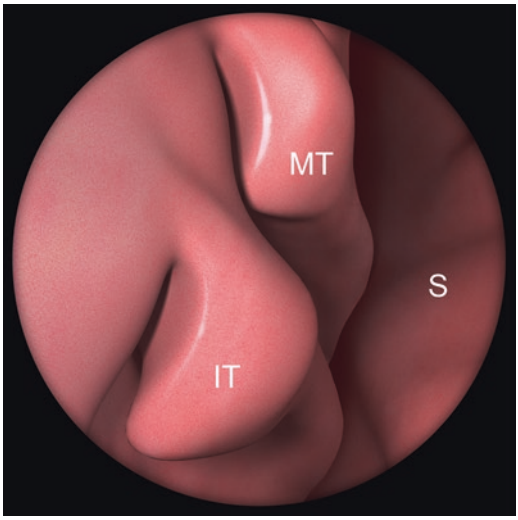

Fig. 11.5 In the initial endoscopic view through the right nostril as one approaches the sella, the inferior turbinate (*IT*) and middle turbinate (*MT*) are seen laterally and the septum (*S*) medially

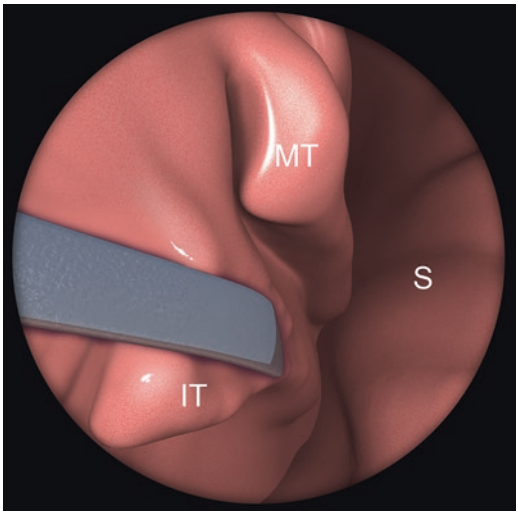

Fig. 11.6 The blunt, curved end of a Cottle elevator is used to out-fracture and lateralize the inferior turbinate (*IT*) to increase the working area and enhance postoperative respiratory function. This maneuver is performed bilaterally, and significantly reduces postoperative nasal constriction and consequent nasal breathing problems

The cocaine pledgets are then removed and the endoscope inserted along the floor of the nasal cavity into the selected nostril. The right nostril will be used for the purposes of this description. The initial anatomy to be appreciated are the inferior and middle turbinates laterally with the nasal septum medially (Fig. 11.5). The first step is to fracture and displace the inferior turbinates laterally on both sides (Fig. 11.6). This fracture and displacement creates an increase in working space; however, the main benefit is to increase airflow and enhance quality of breathing postoperatively [15–18]. Similarly, the middle turbinate on the side of the planned

entry into the sphenoid sinus is fractured and lateralized during the surgery (Fig. 11.7) to significantly enhance the exposure, but in this instance, it is medialized to the original position at the conclusion of surgery. We do not routinely perform a turbinate resection unless anatomic variations or abnormalities such as bulla formation significantly impair the approach. If the middle turbinate is divided and displaced inferiorly for more exposure, care must be taken not to damage the proximal portion of the sphenopalatine artery (SPA) [19]. The superior turbinate is now visible at the superior lateral aspect of the nasal cavity and the medial side can be followed to its base and then posteriorly to aid in identifying the ostium of the sphenoid sinus (Fig. 11.8). Alternatively, the ostium of the sphenoid sinus can be found by following the base of the inferior turbinate to the posterior nasal aperture (choana),

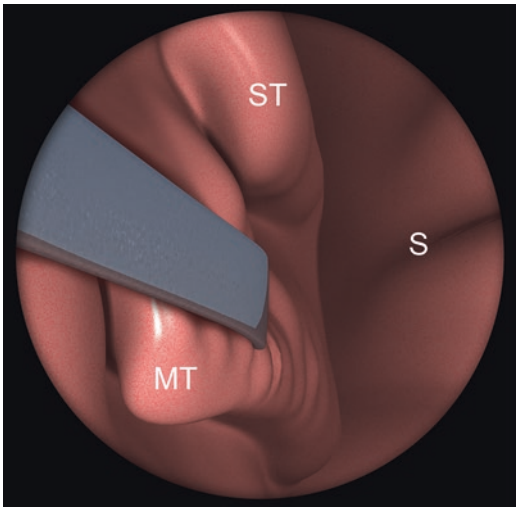

Fig. 11.7 Following lateralization of the inferior turbinate (*IT*), the Cottle elevator is again used to perform the same maneuver on the middle turbinate (*MT*). The superior turbinate (*ST*) now comes into view in the lateral portion of the field superior to the MT

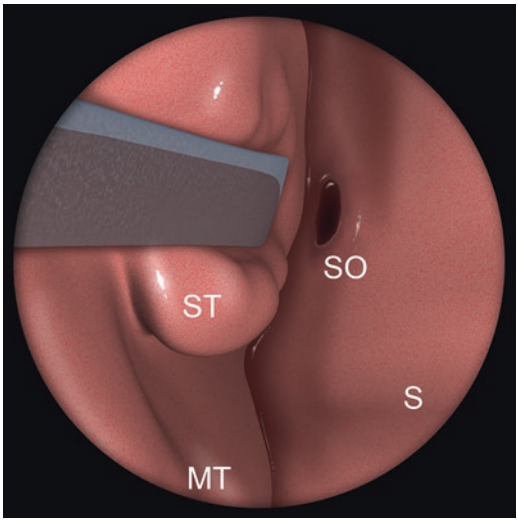

Fig. 11.8 Above the middle turbinate (*MT*), the superior turbinate (*ST*) can be identified and its base is followed posterior to identify the ostium of the sphenoid sinus (SO) medial to the septum (*S*). A Cottle elevator can be inserted into the ostium to verify the location with fluoroscopy

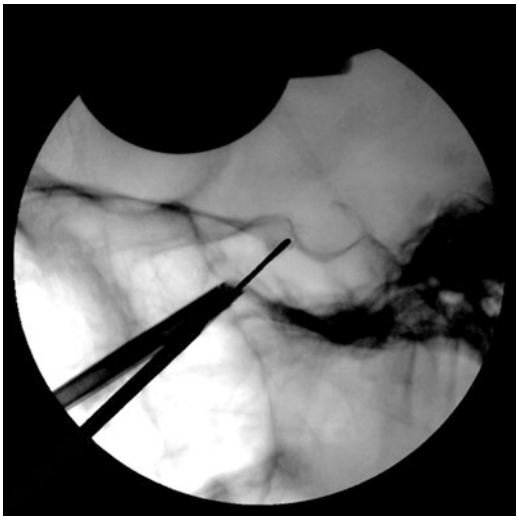

Fig. 11.9 Lateral skull fluoroscopy focusing on the sella while using a Cottle elevator to confirm the entry to the sphenoid sinus

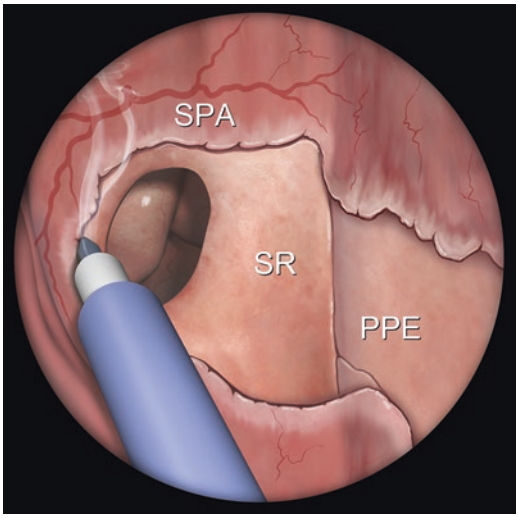

Fig. 11.10 The needle Bovie electrocautery is used to remove the mucosa immediately surrounding the sphenoid ostium and covering the rostrum of the sphenoid sinus (*SR*). The dissection continues medially to expose the junction of the SR with the perpendicular plate of the ethmoid (*PPE*). Care must be taken to avoid the sphenopalatine artery (*SPA*)

which is bordered medially by a midline structure, the vomer, and superiorly by the sphenoid bone. The ostium of the sphenoid sinus is usually 1.5 cm [20] above the superior aspect of the posterior nasal aperture. Occasionally, the ostium can still be difficult to find and a navigation system or intraoperative fluoroscopy is useful as an aid to locate or confirm the location (Fig. 11.9). This usually occurs in the setting of sinusitis and chronic inflammation, where mucosa is thickened and grows over the ostial opening (Video 11.1).

Next needle-tip electrocautery is used to circumferentially cauterize the mucosa immediately around the ostium and more extensively medially along the sphenoid crest, and then inferiorly to expose the junction of the crest with the perpendicular plate of the ethmoid bone (Fig. 11.10). Excessive cauterization laterally or

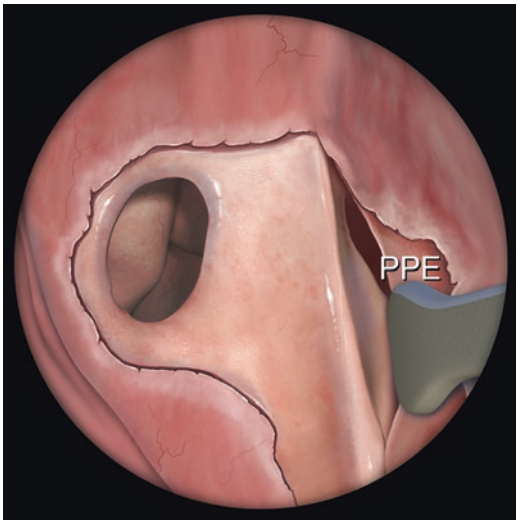

Fig. 11.11 The junction of the sphenoid rostrum and the perpendicular plate of the ethmoid (*PPE*) are separated with the sharp end of the Cottle elevator and a submucosal dissection exposes the contralateral ostium. The PPE must be separated sufficiently to gain wide exposure of the contralateral ostium

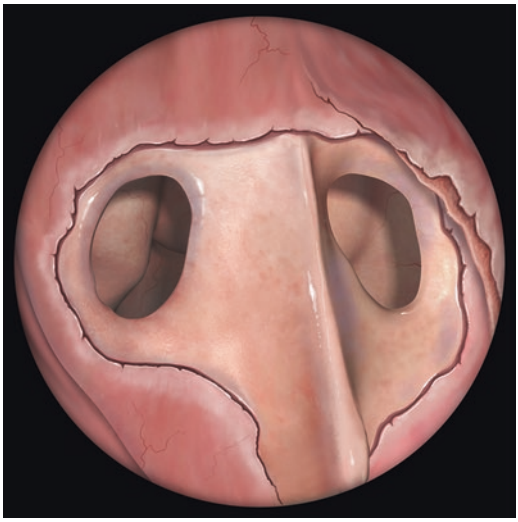

Fig. 11.12 Here the completed dissection is seen with exposure of bilateral sphenoid ostia

inferiorly may sacrifice the sphenopalatine artery. Superiorly, care must be taken to not damage the olfactory mucosa or perforate the thin anterior skull base. A Cottle septal elevator or like instrument is then used to cleanly dissect the mucosa laterally, and then fracture the perpendicular plate of the ethmoid from its junction with the sphenoid crest (Fig. 11.11) away to the contralateral side, exposing the rostrum sphenoidale (Fig. 11.12). Using the Jansen-Middleton cutting forceps, a Hartman Conchotome or drill, bone is removed to connect the two sphenoid ostia into a singular opening (Fig. 11.13). A Kerrison rongeur may then be used to perform partial ethmoidectomies superiorly (Fig. 11.14) and expand the sphenoid sinus circumferentially (Fig. 11.15). Bleeding from branches of the posterior ethmoidal

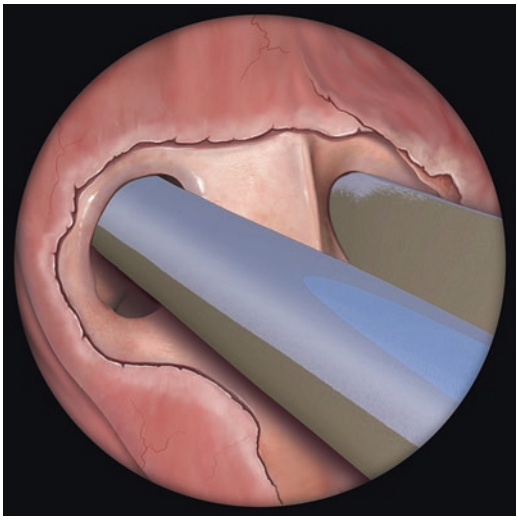

Fig. 11.13 The Jansen-Middleton cutting forceps are used to remove the sphenoid rostrum separating the two ostia, enlarging the opening into the sphenoid sinus. Carefully placing each side of the forceps through the ostia slightly inside the sinus facilitates removal

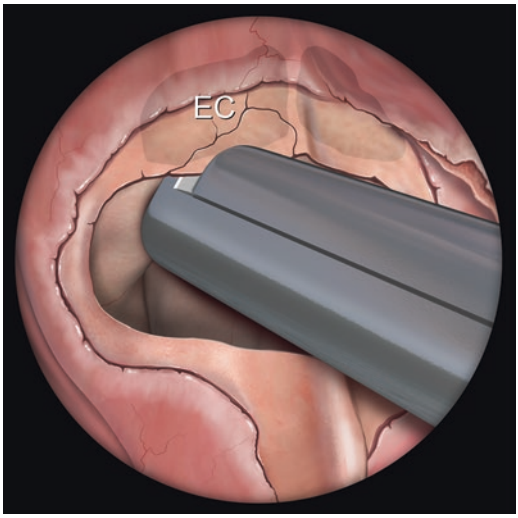

Fig. 11.14 Kerrison or Conchotome rongeurs arethen used to circumferentially enlarge the opening of the sphenoid sinus and to perform a posterior ethmoidectomy, opening the ethmoid air cells (EC). Care must be taken not to exert upward pressure on the planum sphenoidale, as the bone is thin and violation of the dura can occur with vigorous upward pressure

arteries may be encountered and can be managed with judicious use of the needle-tip electrocautery or the bipolar forceps. The mucosa is reflected away from the sphenoid sinus inferiorly and preserved.

Several sphenoid sinus landmarks should be identified including the optic and carotid protuberances which generally demarcate the location of the optic nerves and internal carotid arteries, respectively (Fig. 11.16). There is usually a considerable degree of variation and distortion of the landmarks in both normal and pathological states from variations in sphenoid sinus pneumatization, arterial hypoplasia, and tumors to name a few. A firm understanding of the normal anatomical arrangement is needed before one can grasp the myriad of possible variations. In general,

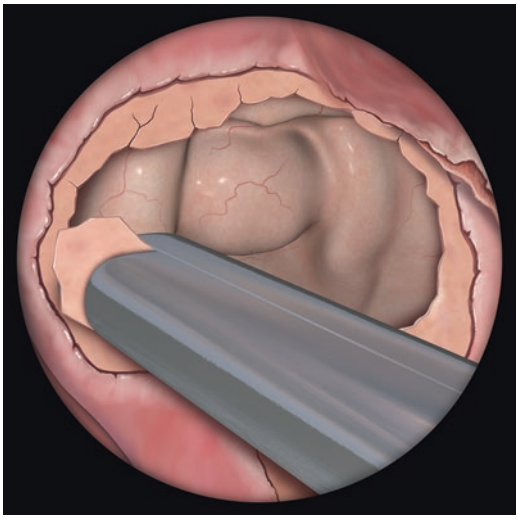

Fig. 11.15 Further bony resection is performed to expand the sphenoid opening laterally. A wide sphenoidotomy is essential to prevent postoperative sphenoid sinusitis

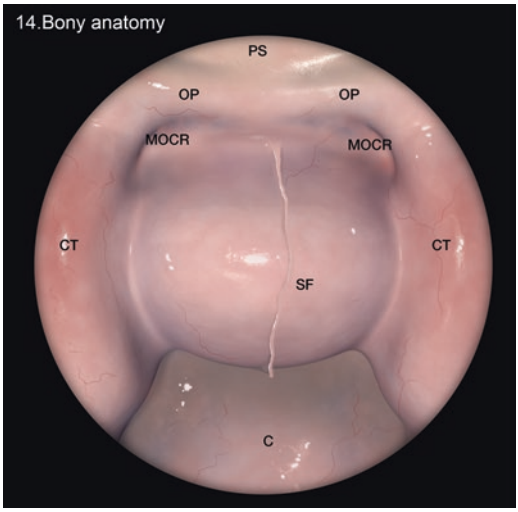

Fig. 11.16 Adequate exposure is achieved once all critical landmarks can be identified including planum sphenoidale (*PS*), optic protuberances (*OP*), medial optico-carotid recess (*MOCR*), carotid tubercles (*CT*), clivus (*C*), and the sella floor (*SF*)

the safest approach is to open the sellar floor in what can best be identified as the center taking into consideration preoperative imaging, preserved midline landmarks such as the rostrum sphenoidale, and fluoroscopic or navigation guidance if available. A reliable way to assess the midline is to line up the columella with the center of the rostrum of the sphenoid sinus. Septations within the sphenoid sinus are not reliable midline landmarks. A micro-Doppler probe can be very helpful in identifying the carotid arteries. The floor of the sella is generally very thin, more so when an adenoma is present, and can usually be breached with gentle pressure from a micro-cup curette. The footplate of a Kerrison rongeur or other instrument can then be used to enlarge the opening in an extradural plane. The senior author strongly

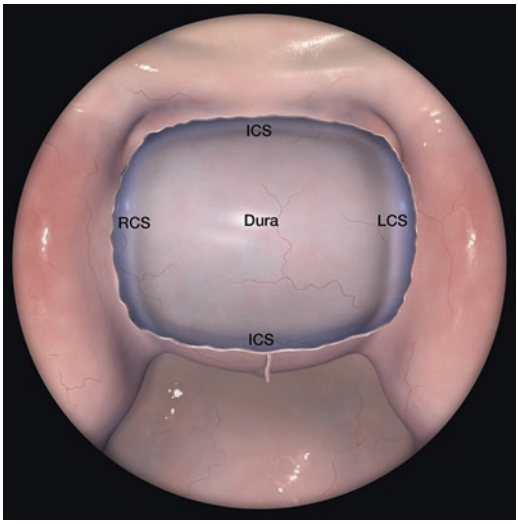

Fig. 11.17 The sella floor is opened centrally and the opening is carefully expanded laterally, superiorly, and inferiorly to fully visualize the left and right cavernous sinus (*LCS* & *RCS*) laterally and the intercavernous sinuses (*ICS*) superiorly and inferiorly. A wide opening is essential

opposes the use of small chisels, for the path and excursion of these instruments cannot be sufficiently well controlled at times. Acromegalic patients are often an exception and cautious drilling is usually required. Our standard exposure enlarges the sella opening extradurally from medial to lateral to visualize the medial edges of both cavernous sinuses and anteriorly and posteriorly to the anterior and posterior intercavernous sinuses, respectively (Fig. 11.17). The intercavernous sinuses have been identified in 80–100% of specimens in cadaver studies [21, 22] but are not always complete. When the intercavernous sinuses cannot be visualized, the anterior exposure stops at the planum sphenoidale and inferiorly and posteriorly at the horizontal portion of the sellar floor at its junction with the upper clivus (Fig. 11.18) (Video 11.2). Many tumors can be resected without visualizing the cavernous sinuses; however, we feel that the safest approach is to be able to visualize the critical structures to preserve them. Making an assumption or educated guess as to the location of the venous sinuses or carotid arteries can lead to costly errors with inadvertent injury.

It is not uncommon to encounter bleeding from the dura surrounding the cavernous and intercavernous sinuses during exposure, or often from an edge of these sinuses that is opened during the dural incision. This bleeding can be quickly controlled with an absorbable hemostatic agent. We favor the use of either Surgicel or Floseal. The key to managing small or large venous hemorrhages is to remain calm and be patient, avoid using large or bulky pieces of hemostatic agents. Apply just enough to cover the area of concern rather than the entire field, followed by an appropriately sized cotton patty. A single cotton patty can be gently held in place or wedged between the hemostatic agent and bony edge until the bleeding stops. Another trick that can be used is to place the hemostatic agent, and then take a tiny piece of bone wax and place it over the material. Then, using a tiny cotton pledget, one can wedge the bone wax against and/or under the bony edge, which will be a

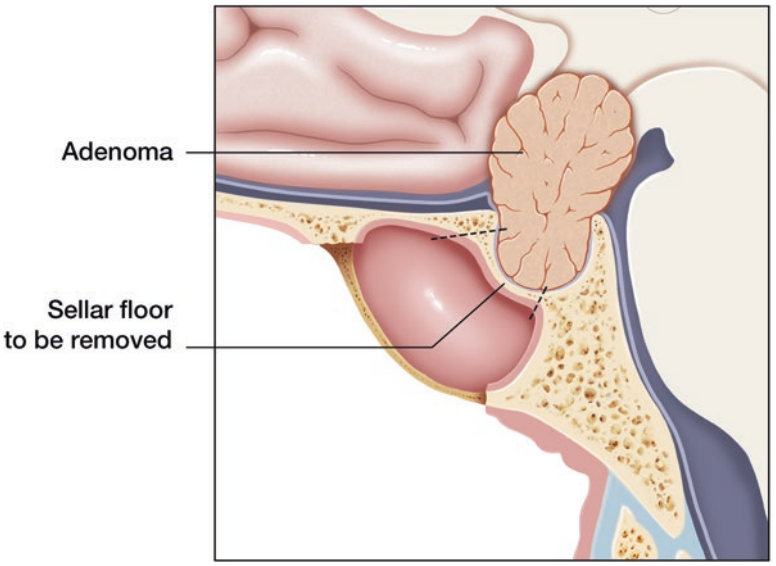

Fig. 11.18 Artist's depiction of a sagittal view of the operative site depicting the extent of sella floor to be removed between the planum sphenoidale and clivus

way to apply continuous pressure to the material underneath it. With patience, bleeding from the venous structures will always stop and the procedure can continue. The magnification created by the endoscope or microscope exaggerates the true rate and volume of bleeding.

We next use the bipolar cautery on the dura in the center of the sella floor and open it sharply with pituitary scissors in a cruciate fashion followed by bipolar cauterization of the dural leaflets. The opening is then expanded in the same manner up to the edge of the venous sinuses. A biopsy is taken followed by tumor resection (Fig. 11.19). Care must be taken to identify the compressed pituitary gland and preserve it; it may often be found posteriorly (Fig. 11.20) (Video 11.3).

We have found a combination of bayonetted Hardy curettes and suction to be most useful. Tumors with significant suprasellar extension can be challenging to achieve a total resection safely. In this instance, provided no CSF leak has been identified, and the sellar portion of the tumor has been resected, we use injection into the lumbar drain to assist in pushing the suprasellar component of the tumor inferior into the sella. The drain has been inserted and constructed as described previously in the chapter and the anesthesiologist has been instructed on the procedure prior to surgery. The anesthesiologist slowly and gently injects 5–10 cc of preservative-free injectable saline at a time as directed by the surgeon. As the intracranial pressure increases from the injection, the tumor is pushed down through the diaphragma sella into the sella where it can be easily and safely resected with direct visualization. The maneuver is repeated as needed. The surgeon constantly monitors and reassesses the situation; if the tumor is not presenting as expected, an equivalent

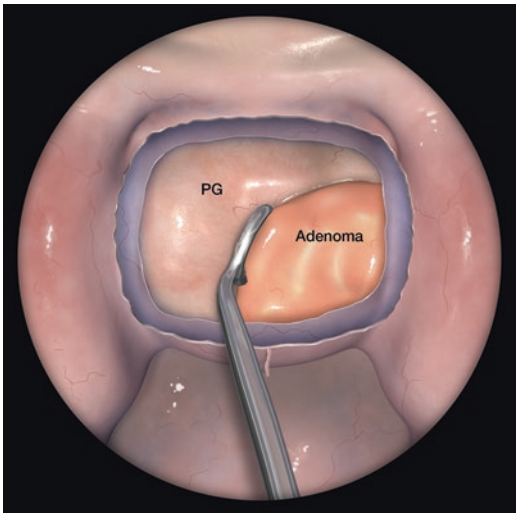

Fig. 11.19 In the case of microadenomas, ringed curettes can be used to help perform an extracapsular dissection of the tumor while preserving the pituitary gland (*PG*)

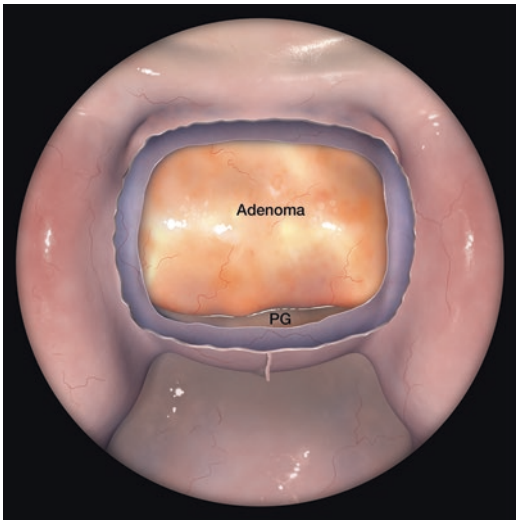

Fig. 11.20 Often times a macroadenoma displaces and compresses the pituitary gland (*PG*) posteriorly

volume of saline is removed, more tumor is resected and then the procedure attempted again. When resection is completed, saline is removed so that the arachnoid membrane is not tense or bulging into the sella (Video 11.4). A CSF leak is not an absolute contraindication to the lumbar drain maneuver but one has to be mindful that injection may enlarge a hole in the arachnoid, and that the period of time with increased pressure will be short, as CSF will leak through the hole and diminish the effectiveness of the maneuver.

Once the resection is felt to be complete, or when visualization is suboptimal because of continued oozing, the operating microscope is then brought into the field looking through a self-retaining nasal speculum for the final stages of tumor resection.

The microscope field of view is limited by the speculum but gives the surgeon better tissue differentiation and depth perception. It is particularly useful to work along the medial edge of the cavernous sinus and skull base, dissecting around the carotid and the cavernous sinus, as well as for inspecting the arachnoid membrane of the suprasellar cistern and arachnoid-cavernous interface. The enhanced tissue differentiation also helps distinguish normal pituitary gland to be preserved from tumor. In many cases the microscope and endoscope can be used alternately and repetitively, until the goal of surgery is achieved.

Following tumor resection, the surgical cavity is then irrigated with absolute alcohol if no CSF leak is present [23, 24]. This chemical cauterization aids in hemostasis and lysis of microscopic rests of tumor cells if present. We have not experienced any complications from this approach but alcohol penetrating any arachnoid defect or opening in the cavernous sinus could result in damage to critical structures [25]. We do not allow the alcohol to remain in the area for more than a 10–15 s, and application is followed by copious saline irrigation to completely wash the alcohol away.

Hemostasis is achieved and the closure begins with reconstruction of the skull base. The previously harvested abdominal fat graft is trimmed to a size that will occupy the cavity created, but not packed so tightly so as to cause compression of the surrounding structures (Fig. 11.21). If there is a CSF leak, a portion of the fat is placed in the hole in the arachnoid to aid in producing a tight seal. The sella floor is then reconstructed with a Medpor polyethylene implant (Stryker; Kalamazoo, MI) that is trimmed to a size just larger than the sellar opening [26]. The implant is wedged between the fat graft and inner dural surface (Fig. 11.22). Absorbable dural sealant material is then sprayed over the area of reconstruction (Figs. 11.23 and 11.24) and the sphenoid sinus mucosa is replaced if preserved (Video 11.5).

We have found that a nasal-septal flap is not necessary to repair most intraoperative CSF leaks, as long as one can get fat up against the hole in the arachnoid and

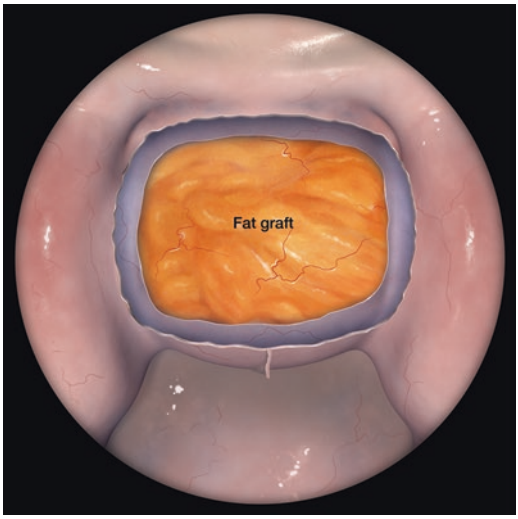

Fig. 11.21 Reconstruction of the sella floor begins with placing a fat graft large enough to fill the void previously occupied by tumor

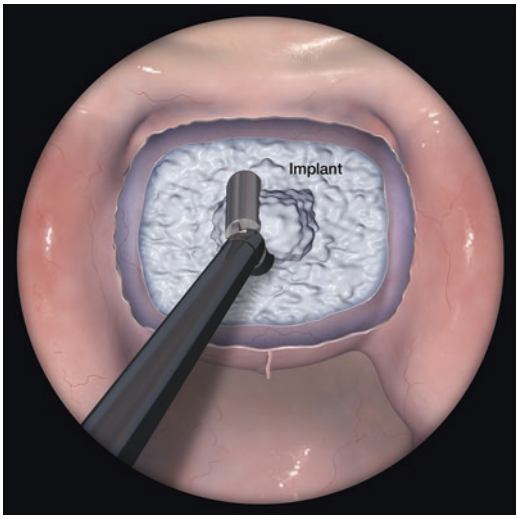

Fig. 11.22 The Medpor implant is placed deep to the dural so that it is affixed between the fat graft and dura and held in place by the overlying dural edges. If insufficient dura is available, it can be wedged deep to the bone opening

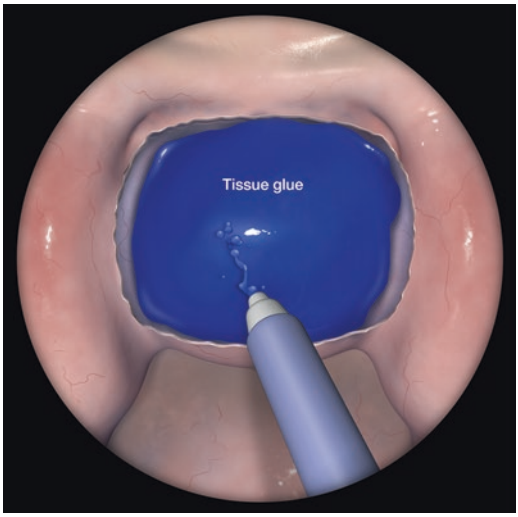

Fig. 11.23 Tissue glue is placed over the Medpor implant to complete the reconstruction

preferably through it as a type of tissue plug, and one can get a tight reconstruction with the Medpor graft held firmly in place either by dura and/or bone. We take great care to use precise carpentry when shaping and placing the graft, so the fat is held firmly in place, and the chance of the Medpor dislodging is minimal. In cases where it is difficult to get good purchase intradurally, the Medpor is placed extradurally and tightly lodged and held into place by shaping it so it fits under the bony edges of the opening in all directions.

While many believe that reconstructing the skull base in the absence of a CSF leak is not mandatory, we feel that it creates a biologic barrier to infection and reduces the risk of optic chiasm herniation in the future by ensuring that the fat graft

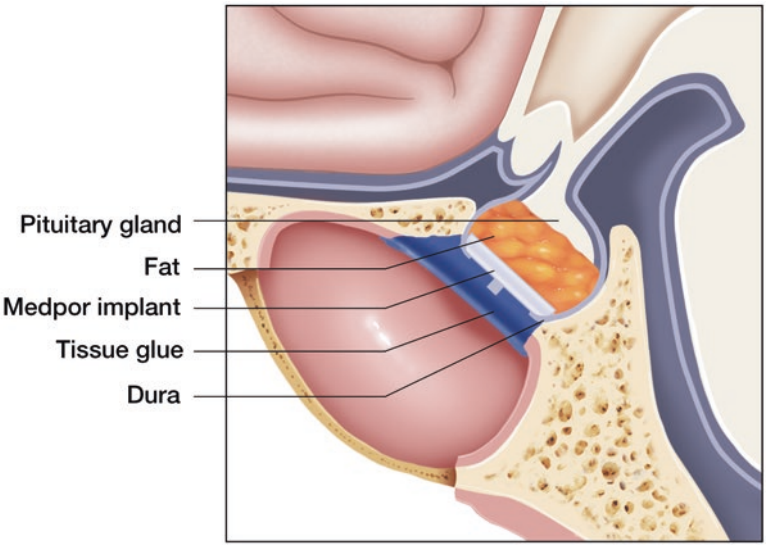

Fig. 11.24 Artist's depiction of a sagittal view of the skull base reconstruction demonstrating the Medpor implant between the fat and dural, covered by tissue glue

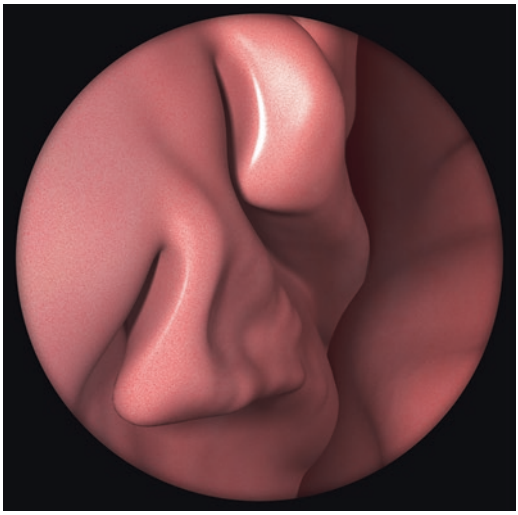

Fig. 11.25 At the conclusion of the procedure, the middle turbinate (*MT*) is restored to its original position while the inferior turbinate (*IT*) remains lateralized. Failure to restore the middle turbinate to its anatomic position can lead to ethmoid sinusitis

remains in place. Moreover, it produces a universally watertight closure, in case there is a CSF leak that was not identified at the time of surgery.

When skull base reconstruction is complete, the middle turbinate is returned to its original position and the approach corridor is inspected for good hemostasis (Fig. 11.25). The septum and perpendicular plate of the ethmoid are returned to midline. Septal deviations that are obvious are repaired by resecting the appropriate amount of bone and cartilage. The inferior turbinates remain lateralized as

previously discussed. The external nares are then inspected for mucosa tears that can be repaired with absorbable suture. We do not use any form of nasal packing at the end of the procedure. Only a small piece of cotton gauze taped externally is placed until the following morning to catch any anterior drainage. The throat pack is removed while suctioning with a Yankauer suction tip to ensure that no blood remains, which greatly lessens the likelihood of postoperative nausea and vomiting.

Postoperative Care

We observe our patients in the intensive care unit for at least one night after surgery and the lumbar drain remains in place. If no CSF leak was seen at the time of surgery, the drain remains closed overnight and removed the following morning after confirming the absence of a leak. If a CSF leak is observed during surgery, the drain remains closed for 6 h before opening at the level of the shoulder. Closing initially allows intracranial pressure to normalize, increases the pressure at the surgical site, and may tamponade any venous bleeding that may occur. Additionally, it reduces the risk of over drainage with nursing staff that may be unfamiliar with the device in the recovery room. Should a CSF leak require diversion, we typically drain for 3 days prior to closing the drain and observe for a leak prior to removing it. We also begin treatment with antihistamines, decongestants, and gentle saline nasal flushes on the first postoperative day. Routine considerations for pituitary surgery patients are also implemented including monitoring urine output specific gravity, and sodium levels.

Conclusion

The technique for transnasal transsphenoidal pituitary surgery involves approaching the sphenoid sinus, expansion of the sinus opening, entry into the sella, tumor resection, and reconstruction. There are many nuances and variations to the procedure that should be tailored to the pathology and to the patient. The endoscope and microscope are complementary tools, each with unique capabilities. The majority of neurosurgeons have used the operating microscope for decades and are extremely comfortable with its view. The endoscope is relatively newer to the field, but is now standard in many centers and training programs.

The endoscope provides a sharp, clear picture with excellent illumination. The endoscope is not constrained by a nasal speculum in its line of sight, and angled scopes can help view around edges of structures (Fig. 11.26). The angled view and shorter distance from lens to tissue is particularly advantageous when dissecting within the suprasellar cistern. These benefits are reduced with tumors restricted to the sella. The endoscope does require a holder whether mechanical or in the form of an assistant, and occupies precious space in the constrained nasal passage limiting instrument movement. These limitations are diminished with experience and practice but not removed altogether.

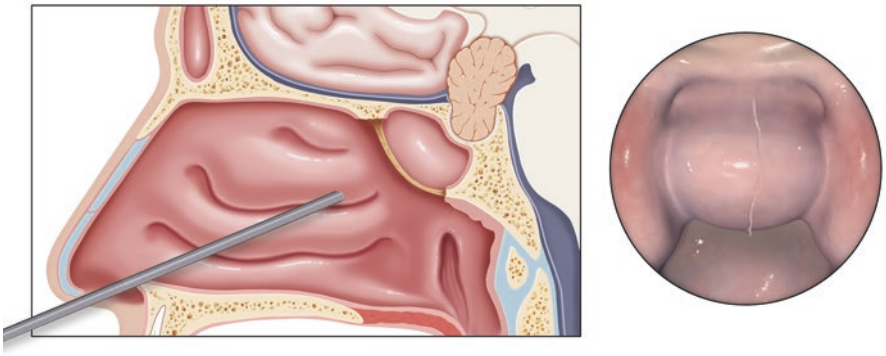

Fig. 11.26 Artist's depiction of the position of the endoscope camera during a transnasal transsphenoidal operation (*left*) and the field of view seen through this instrument (*right*)

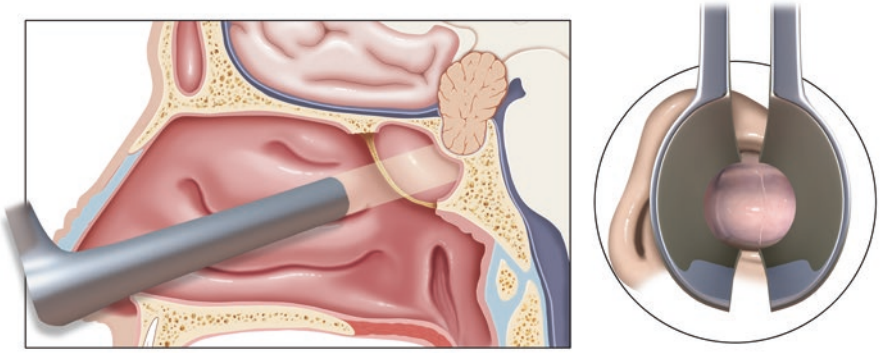

Fig. 11.27 Artist's depiction of the microscopic portion of a transnasal transsphenoidal operation with the position of the nasal speculum (*left*) and the field of view seen with the microscope (*right*)

Operating microscopes also provide a sharp, clear picture but with a three-dimensional view and superior tissue differentiation (Fig. 11.27). It does not require a holder and the increased distance from the lens to the operative site eliminates problems of fogging, smudging, or contact with blood. The line of sight is constrained by the need for a nasal speculum limiting the surgeon's field of view. We find that the enhanced tissue differentiation is particularly helpful when clearing tumor from normal gland or clearing the wall of the cavernous sinus. The improved depth perception is also advantageous when removing tumor around the carotid artery or within the cavernous sinus.

Endoscopic and microscopic techniques for pituitary surgery are not adversarial, but rather complementary. Surgeons should be trained in both techniques and versatile enough to switch back and forth between each modality during each surgical procedure, as the clinical situation dictates.

Acknowledgments This work was supported by the Donna and Kenneth R. Peak Foundation, The Kenneth R. Peak Brain and Pituitary Treatment Center at Houston Methodist Hospital, The Taub Foundation, The Blanche Green Estate Fund of the Pauline Sterne Wolff Memorial Foundation, The Verelan Foundation, The John S. Dunn Foundation, The Houston Methodist Hospital Foundation, The Kelly Kicking Cancer Foundation, The American Brain Tumor Association, the senior author's referring physicians who have allowed us to gain knowledge of the many nuances of this surgery, and the many patients and families who have been impacted by the devastating effects of brain and pituitary tumors. We also thank Nyla Ismail, Ph.D. and Megan Fulin for editorial support and assistance.

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Transcranial Approaches to the Sellar and Parasellar Areas

12

Bradley N. Bohnstedt, Todd Eads,
Jonathan Weyhenmeyer, and Aaron A. Cohen-Gadol

Introduction

The pathology of the parasellar space is composed of a large number of potential diagnoses owing to the vast morphology of structures comprising the region. Often, parasellar lesions extend superiorly and/or laterally from the sella, e.g., pituitary adenoma or carcinoma, and engulf adjacent structures such as the cavernous carotid laterally or the optic chiasm superiorly. Still other pathologies stem from the embryonic Rathke's cleft such as the craniopharyngioma and Rathke's cleft cyst. The differential diagnosis for a space-occupying lesion includes, but is not limited to, metastasis, infection, intraaxial brain tumor with extension and meningioma, epidermoid cyst, dermoid cyst, teratoma, germinoma, and neurocysticercosis. While each of these pathologies is unique, the options for surgical resection can be grouped into two overarching surgical approaches: transsphenoidal surgery and transcranial surgery.

As with all forms of neurological surgery, approaches to the pituitary were initially fraught with difficulty and had high rates of morbidity and mortality [5]. The first attempt at surgical resection of a parasellar mass lesion occurred in 1893 via a

B.N. Bohnstedt, MD
Department of Neurosurgery, Oklahoma University Health Sciences Center, Oklahoma City, Oklahoma, USA

T. Eads, MD
Department of Neurological Surgery, Goodman Campbell Brain and Spine, Indiana University, Indianapolis, IN, USA

J. Weyhenmeyer, MD
Neurosurgery Resident, Goodman Campbell Brain and Spine, Indiana University School of Medicine, Indianapolis, IN, USA

A.A. Cohen-Gadol, MD, MSc (✉)
Department of Neurosurgery, Indianapolis Methodist Hospital, Indianapolis, IN, USA
e-mail: acohenmd@gmail.com

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_12

transcranial approach utilizing a method that had been postulated by Sir Victor Horsley [5]. The surgery was a failure as the region was never reached and the patient subsequently died. While Horsley's mortality rate for transcranial access to the sella approached 20%, his surgical colleagues had mortality rates close to 50–80% [4, 11]. As such, attempts were made to access the sella and parasellar spaces via other means. The transsphenoidal approaches were subsequently developed and initially carried a much lower rate of patient mortality. However, the initial transsphenoidal techniques were limited by the technology and medical knowledge of the time as there was no operating microscope and the operating field was often dark due to poor lighting [5]. In addition, patients often suffered from cerebrospinal fluid (CSF) leaks and developed raging meningitis that resulted in mortality as antibiotics had not yet been discovered. Realizing the difficulties of transsphenoidal surgery and some of the limitations in adequately decompressing the optic apparatus, Harvey Cushing attempted transcranial approaches. It was not until the advent of the operating microscope that the transsphenoidal approach regained its popularity in the neurosurgical community [5]. Recently, with the advent of angled endoscopes and endoscopic microsurgical instruments, the endoscopic endonasal transsphenoidal approaches are considered far superior routes for most tumors within the sellar and parasellar regions.

While endoscopic endonasal transsphenoidal approaches are preferred for most parasellar lesions, there is a subset of lesions, approximately 1–4%, that necessitate surgical resection via a transcranial route. This is largely due to the morphology of the lesion and its relationship to surrounding structures. Pituitary tumors with extensive superior parasellar extension may not readily descend into the sellar space, inhibiting significant resection from an inferior approach. Parasellar lesions extending into the cavernous sinus and dumbbell-shaped sellar lesions with a narrow neck across the diaphragma sellae may be preferably approached through a transcranial route. In addition, patients may have contraindications to transsphenoidal surgery such as active sinus infection, adjacent vascular disease including arteriovenous malformation, or cerebral aneurysm. Patients with ectatic "kissing" carotid arteries are at high risk during an endonasal route.

In addition, the morphology of the tumor may make it difficult for transsphenoidal resection, e.g., fibrous tumors that are highly vascular with significant parasellar extension may complicate their removal via an inferior to superior trajectory. Transcranial approaches are most frequently attempted after a previously failed transsphenoidal exploration for any of the previously mentioned reasons. Importantly, there are a subset of parasellar lesions that do not enlarge the sella, but instead grow and encompass the surrounding neurovascular structures, e.g., craniopharyngiomas and meningiomas. The surgeon must plan for these lesions by using either an extended endonasal or a transcranial approach. Either method will allow for a much greater field of view and thus an improved extent of resection. Finally, one must take into account how the parasellar lesion encompasses the surrounding neural structures, e.g., optic chiasm, cavernous sinus, and cranial nerves. The way the lesion encompasses these structures can dictate which type of approach is warranted.

As noted above, transcranial approaches provide a large field of view and very flexible working angles and expose the cranial nerves and neurovascular anatomy early in the operation. For example, during the subfrontral approaches, the optic nerves and carotid arteries are quickly identified after initial dural opening. This fact provides the surgeon optimum opportunity to protect these structures during the dissection and tumor resection. While the outcomes associated with transcranial approaches have greatly improved over the past century, they continue to present increased surgical risks of a craniotomy including frontal lobe injury due to retraction. When deciding on an approach to the sellar and parasellar regions, the benefits of each approach should be carefully weighed against each approach's inherent risks. When the operator decides on a particular transcranial approach, he or she must take into account the specific features of the pathoanatomy including its size, location, relationship to the critical neurovascular structures, and the predicted pathology.

Surgical Considerations

For all approaches described here, the head is placed in a 3-pin Mayfield head holder. The head is positioned above the heart to encourage venous drainage, turned 20–30° contralaterally, and slightly extended to keep the zygomatic arch, the tip of the malar eminence, as the highest point in the surgical field (Fig. 12.1). A minimal amount of hair is shaven, and the planned skin incision is infiltrated with lidocaine/epinephrine solution.

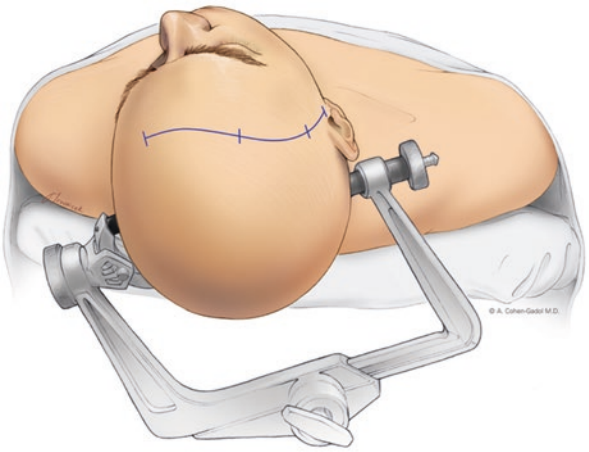


Fig. 12.1 The head is held in position via a 3-pin Mayfield head holder. The head is positioned above the heart to encourage venous drainage, turned 20–30° contralaterally, and slightly extended to keep the malar eminence as the highest point in the surgical field (Used with permission from The *Neurosurgical Atlas* by Aaron Cohen-Gadol, MD)

Pterional Approach

The pterional approach provides excellent access to the anterior and middle cranial fossa such that it has become the workhorse approach for transcranial procedures. Yaşargil has refined and described the intricacies of this approach [14]. The pterional approach provides excellent access to the sellar and parasellar spaces. Of the transcranial approaches, it commonly affords one of the shortest operating distances to the lesion [3]. The senior author (ACG) most commonly employs the extended pterional approach, described below, which may provide even greater access to the anterior and middle cranial fossae.

As with all craniotomies, the laterality of the entry point should be carefully selected. The most important determinant of approach laterality is the side of the tumor. Ideally the tumor should be approached from the side on which the tumor resides or the side on which most of the tumor is located as this will aid in preventing untoward retraction. For tumors that do not significantly extend toward either side, deficits in vision should be noted and the side with greater visual deficit should be the side from which the lesion is approached. If tumor location and vision are indeterminate selectors, then the nondominant hemisphere should be used for the approach, generally the patient's right side. Some colleagues have advocated the use of the contralateral subfrontal route for lesions that are underneath the optic nerve as this operative trajectory can minimize the risk of nerve retraction.

The pterional incision extends from the superior portion of the zygomatic arch toward the contralateral midpupillary line. The incision should be kept behind the hairline when possible as this is cosmetically pleasing and also serves to protect the frontalis portion of the facial nerve anteriorly and the superior temporal artery (STA) posteriorly. The incision is classically begun 1 cm anterior to the tragus to avoid early damage to the STA (Fig. 12.2). The hair occupying the location of the incision should be shaved. Some surgeons may opt for a minimal shave technique where approximately 2 cm of hair, 1 cm on either side of the incision, are removed.

First, the incision is begun on the contralateral side working toward the ipsilateral zygomatic arch. The first portion of the incision should incise the scalp down to the bone. As the skin is incised, bovie electrocautery and Rainey clips promote hemostasis. The incision is continued at the level of the bone until the superior temporal line is reached, at which point a more superficial incision should be made down to the level of the superior fascial layer covering the temporalis muscle. Next, the superior temporal artery is identified and the frontal and parietal branches are dissected. The parietal branch of the superior temporal artery is preserved and the frontal branch is ligated. When reflecting the skin flap forward, the surgeon should keep the plane of dissection below the plane of the superficial fat pad that rests above the temporal muscle and fascia. The frontal branch of the facial nerve travels through the superficial fascia of the fat pad and keeping the dissection below this plane serves to protect this branch. The temporalis muscle is elevated from the bone using bovie electrocautery and reflected with the scalp flap anteriorly in one musculocutaneous layer using fish hooks for retraction (Fig. 12.3). A small cuff of muscle or superior temporal fascia should be left posteriorly to provide a place to which the temporalis muscle can be sutured at the end of the case during closure.

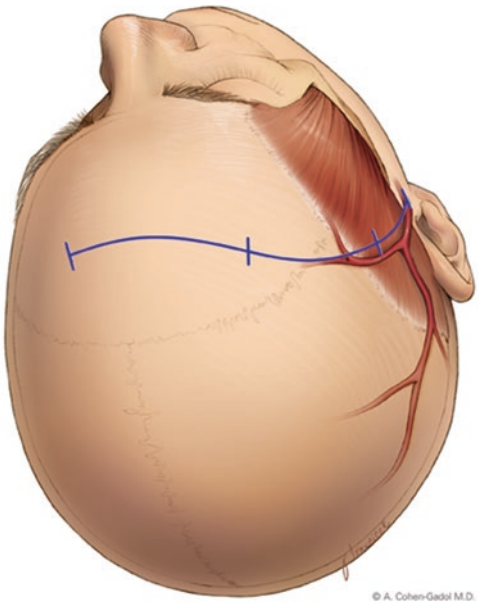


Fig. 12.2 A small area of hair is shaved along a standard pterional skin incision. The incision is begun at the zygomatic arch, 1 cm anterior to the tragus to avoid the superficial temporal artery, and is continued 1–2 cm behind the hairline to the contralateral midpupillary line (Used with permission from The *Neurosurgical Atlas* by Aaron Cohen-Gadol, MD)

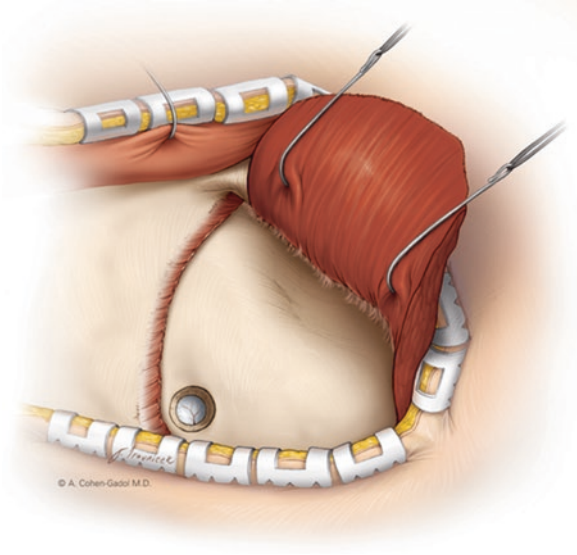


Fig. 12.3 The temporalis muscle is elevated from the bone using bovie electrocautery and reflected with the scalp flap anteriorly in one musculocutaneous layer. The burr hole is placed posteriorly along the course of the superior temporal line (Used with permission from The *Neurosurgical Atlas* by Aaron Cohen-Gadol, MD)

The craniotomy begins with a burr hole placed just inferior to the posterior aspect of the superior temporal line. The burr hole should be placed close to the skin incision to allow for optimum usage of the space provided by the mobilization of the myocutaneous flap. A second burr hole is optional and may be placed at the keyhole or posterior zygomatic arch. After placement of the burr hole, a B1 bit is used to complete the anterior portion of the craniotomy. Upon reaching the sphenoid ridge,

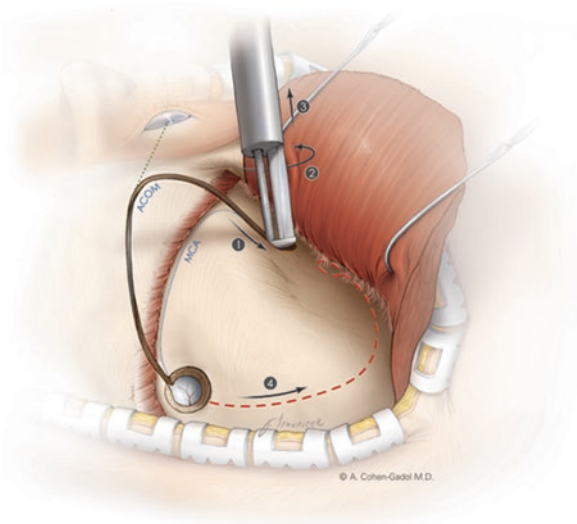
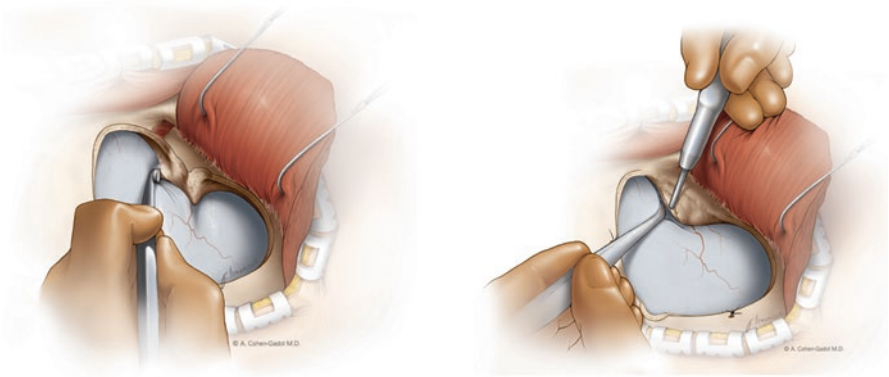


Fig.12.4 A burr hole is placed just inferior to the posterior aspect of the superior temporal line, abutting the skin incision, and a standard pterional craniotomy flap is elevated and extended just lateral to the midpupillary line (Used with permission from The *Neurosurgical Atlas* by Aaron Cohen-Gadol, MD)

the drilling will often become more difficult and further progress by the craniotome may be halted. The craniotome should then be removed and the posterior aspect of the craniotomy should be performed such that the two portions of the craniotomy meet around the lateral sphenoid wing. Finally, a standard pterional craniotomy flap is elevated with a Penfield dissector to release the dura from the underneath surface of the bone flap (Fig. 12.4). If the frontal sinus is violated, it is exenterated by thoroughly stripping its mucosa away to avoid formation of a mucocele, and the sinus ostium is plugged with pieces of temporalis muscle to avoid postoperative cerebrospinal fluid (CSF) rhinorrhea. Additionally, a pericarnial graft should be harvested and placed over the violated sinus at the end of the procedure.

The extended pteriornal craniotomy involves two additional steps that serve to maximize exposure and minimize frontal lobe retraction. First, the lateral aspect of the sphenoid ridge is drilled away to the level of the superior orbital fissure. Second, the edge of frontal bone over the lateral aspect of the roof of the orbit is drilled flush with the roof of the orbit using a high-speed drill (Figs. 12.5 and 12.6). The roof of the orbit may also be drilled to create additional subfrontal space to minimize frontal lobe retraction. Upon achieving adequate boney exposure, the dural incision is made. The incision should be C-shaped with the base of the dural flap left anteriorly, permitting an anterior reflection of the dura in the same manner as the myocutaneous scalp flap (Fig. 12.7). The dural flap is kept in place by dural tack-up sutures, usually three sutures are adequate, that are placed as close to the brain as possible to further increase the working space. Additional dural tack-up sutures may be placed around the dural incision to prevent epidural blood from entering the field.

After opening the dura, the operating microscope is brought into the field and arachnoid dissection is begun. Using the operating microscope, a retractor blade is gently placed subfrontally just anterior to the sphenoid ridge and lateral to the olfactory tract (Fig. 12.8). The olfactory tract is followed posteriorly until the arachnoid



Figs. 12.5 and 12.6 To maximize exposure and minimize frontal lobe retraction, the lateral aspect of the sphenoid ridge is drilled away as far as the superior orbital fissure. The edge of frontal bone over the lateral aspect of the roof of the orbit is drilled flush with the roof of the orbit using a high-speed drill (Used with permission from The *Neurosurgical Atlas* by Aaron Cohen-Gadol, MD)

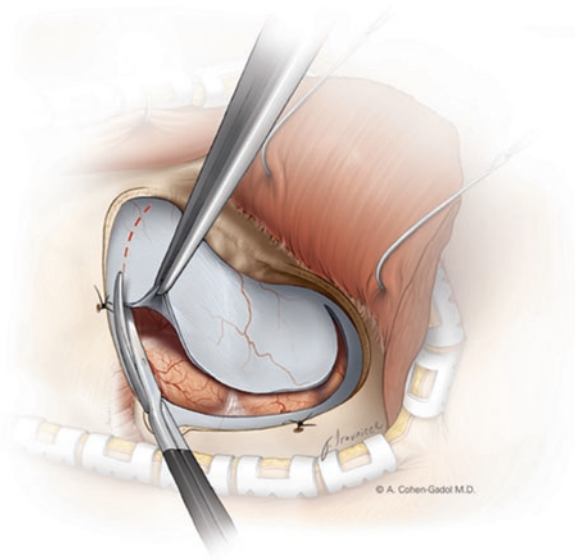


Fig. 12.7 The dura is incised. The surgeon should always be aware of the location of the scissors tips. A C-shaped incision is performed to allow the dura to be reflected anteriorly (Used with permission from The *Neurosurgical Atlas* by Aaron Cohen-Gadol, MD)

over the optic nerve and the internal carotid artery cisterns are identified. In general, it is best to avoid violating the arachnoid directly on the optic nerve so as to prevent injury. Dissecting the opticocarotid and carotid-oculomotor triangles allows for the draining of cerebrospinal fluid and further brain relaxation. As mentioned previously, large tumors in the basal cisterns will inhibit the drainage of CSF and thus prevent adequate brain relaxation. In these instances, preoperative placement of a lumbar drain or intraoperative placement of an external ventricular drain may be performed. Intraoperative placement of an external ventricular drain may be done

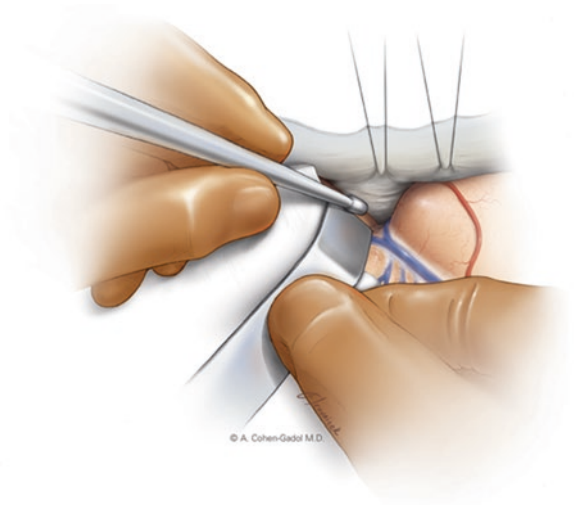


Fig. 12.8 Using an operating microscope, a retractor blade is gently placed subfrontally just anterior to the sphenoid ridge and lateral to the olfactory tract (Used with permission from The *Neurosurgical Atlas* by Aaron Cohen-Gadol, MD)

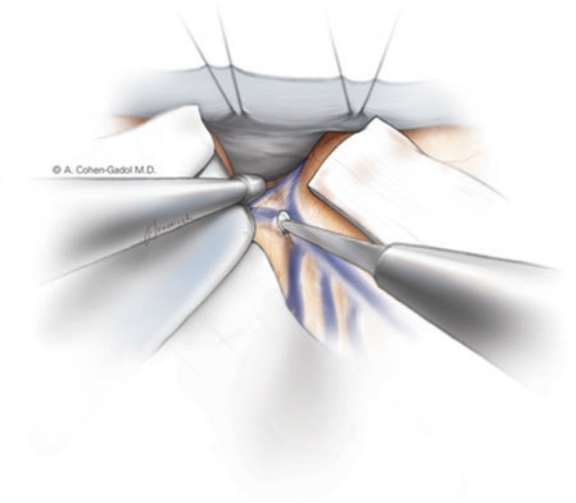
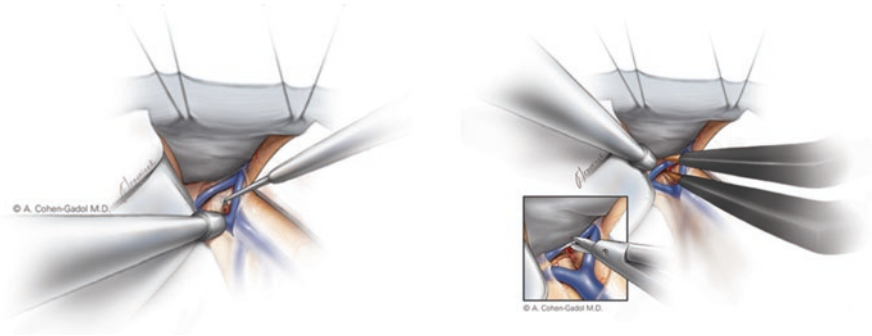


Fig. 12.9 Retraction of the frontal and temporal lobes can be facilitated by opening the anterior limb of the sylvian fissure (Used with permission from The *Neurosurgical Atlas* by Aaron Cohen-Gadol, MD)

through a burr hole or through Payne's point if the surgeon fails to realize the difficulty of brain relaxation prior to the procedure. Either method will greatly increase the ability to mobilize the frontal lobe for increased tumor exposure.

Frontal and temporal lobe mobilization is performed in a stepwise process, accomplished by opening the anterior limb of the sylvian fissure (Fig. 12.9). Opening the anterior limb of the fissures aids in reducing the retraction forces needed to obtain adequate tumor exposure. The dissection of the arachnoid over the anterior limb of the sylvian fissure should proceed in a superficial to deep manner (Figs. 12.10 and 12.11). The arachnoid layers nearest to the tumor must be opened so that optimal exposure of the tumor is obtained (Fig. 12.12) [12]. Arachnoid



Figs. 12.10 and 12.11 The arachnoid of the sylvian fissure is dissected in a superficial to deep manner along its anterior limb (Used with permission from The *Neurosurgical Atlas* by Aaron Cohen-Gadol, MD)

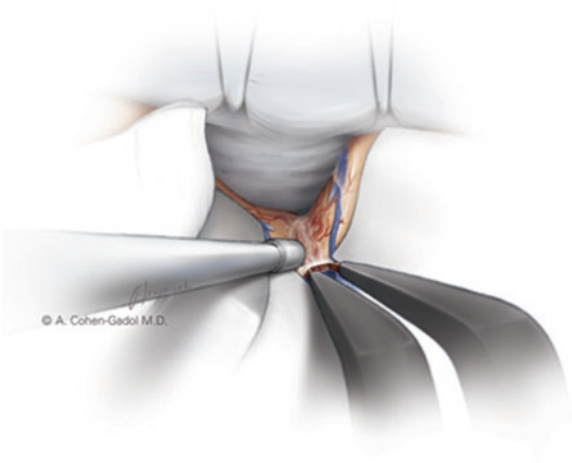
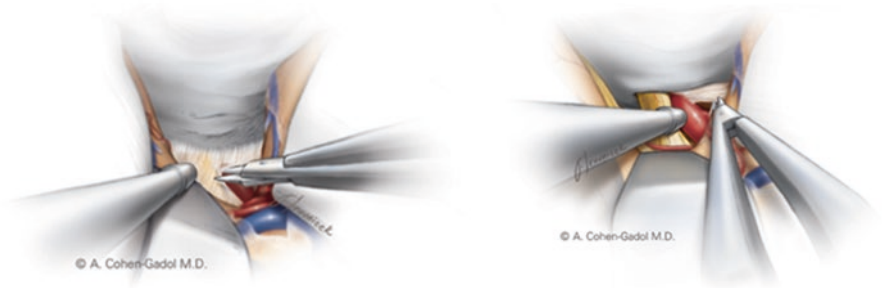


Fig. 12.12 The opening of the arachnoid nearest to the lesion is of key importance for optimal exposure (Used with permission from The *Neurosurgical Atlas* by Aaron Cohen-Gadol, MD)

dissection is continued primarily with sharp dissection methods. It is reasonable to use the microscissors as a dissector, a spreader, and a scissor. This allows for a single instrument to be used for the majority of the dissection and saves surgical time associated with switching instruments. Conversely, the dissection may be performed with a blunt fine-tip probe to separate the arachnoid from the entangled vessels. Small bursts of venous bleeding are frequently encountered and can generally be controlled with irrigation; however, the small bridging veins along the anterior limb of the sylvian fissure may be coagulated with limited consequence to patient outcome. Sylvian arteries should be preserved with their corresponding lobe as much as possible. The extent to which the fissure is split is dependent upon and tailored to the size of the lesion. The thicker arachnoid layers over the carotid artery and optic nerve are sharply cut, but fine arachnoid membranes overlying the optic nerve should be left alone to prevent injury to the nerve (Figs. 12.13 and 12.14).



Figs. 12.13 and 12.14 The thicker arachnoid layers over the carotid artery and optic nerve are sharply cut. Fine layers covering the optic nerve should be preserved to avoid injury (Used with permission from The *Neurosurgical Atlas* by Aaron Cohen-Gadol, MD)

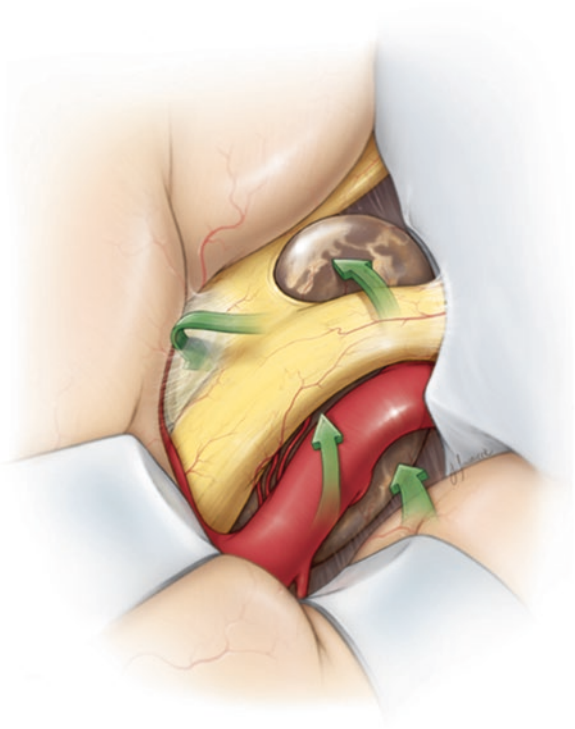


Fig. 12.15 The surgeon can work in a number of different corridors to access and resect the tumor, including the opticocarotid, prechiasmatic, and retrocarotid windows (Used with permission from The *Neurosurgical Atlas* by Aaron Cohen-Gadol, MD)

At this point, the surgeon can work in a number of different corridors to access and resect the tumor, including the opticocarotid, prechiasmatic, and retrocarotid windows (Fig. 12.15). The lamina terminalis, found posterior to the optic chiasm, provides access to the third ventricle and may be entered to resect the tumor with third ventricular extension. Initially, only the ipsilateral optic nerve may be in view, but as tumor resection proceeds, identification of the contralateral carotid artery and optic nerve early in the dissection process is imperative to prevent their injury.

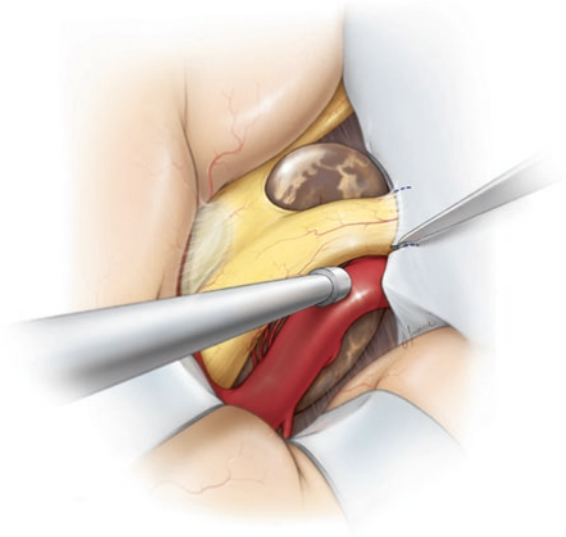


Fig. 12.16 Opening of the falciform ligament will partly release the optic nerve and allow safer mobilization of the nerve to manipulate the tumor (Used with permission from The *Neurosurgical Atlas* by Aaron Cohen-Gadol, MD)

Opening of the falciform ligament will partly release the optic nerve and will allow safer mobilization of the nerve to manipulate the tumor. Tumor resection should begin by devascularization (especially for meningiomas) and intracapsular debulking. Once the tumor is sufficiently debulked, the tumor capsule should be safely dissected away from the critical surrounding tissues. Further details concerning the treatment of individual pathologies can be found in other chapters (Fig. 12.16).

The major disadvantage of the pterional approach is in cases in which the optic chiasm is prefixed, allowing for a very limited working channel. In addition, resection may become more difficult if the lesion extends far superiorly or posteriorly because of limited exposure through this basal frontal route. Complications associated with the pterional approach include infection, hematoma, cerebrospinal fluid leakage, postoperative seizures, and frontal lobe edema from excessive retraction. Optic nerve damage may occur during surgery as a result of aggressive tumor resection or bipolar cautery of the nearby perforating vessels. The perforating arteries supplying the optic apparatus arise from the anterior communicating artery and from underneath the chiasm and should be preserved. Hypothalamic and/or pituitary damage can also occur due to manipulation of these structures or their vascular supply. Pituitary dysfunction may manifest postoperatively as diabetes insipidus and should be treated accordingly.

Orbitozygomatic Approach

The orbitozygomatic (OZ) approach should be thought of as an extension of the pterional craniotomy whereby additional osteotomies superior and lateral to the orbit are performed to increase the intracranial exposure. The OZ exposure provides

a decreased working distance and improved trajectory to the lesion. The modified OZ craniotomy is adequate for reaching parasellar lesions and is the preferred approach when additional bony removal is necessary for resection of large lesions with superior and posterior extensions. Explicitly, the approach is best utilized in patients with lesions that extend superiorly into the third ventricle or anteriorly into the posterior third of the orbit. The modified OZ approach is actually an extended frontotemporal craniotomy that includes a supraorbital osteotomy. Overall, this craniotomy provides an expanded corridor to reach lesions involving the circle of Willis, including the orbit, paraclinoid and parasellar locations, cavernous sinus, and especially the more cranially located basilar apex region.

As with the pterional craniotomy, the head is rotated approximately 15° toward the opposite side and locked into position with Mayfield head holder. The head is slightly extended such that the malar eminence is the most superior aspect of the surgical field. Lesions that are located more medially require less head rotation while lesions located more laterally require greater degrees of rotation. The incision begins no more than 1 cm inferior to the zygoma and within 1 cm of the tragus. The incision is continued behind the hairline, perpendicular to the ipsilateral superior temporal line, to the contralateral midpupillary line where it stops just posterior to the anterior hair line. The periosteum and superficial layer of the temporalis fascia (including the fat pad) are carried up in one layer with the skin flap using a subfascial dissection method to protect the facial nerve which is located within the superficial temporal fascia. The supraorbital notch and supraorbital nerve should be identified at the orbital rim. If the supraorbital nerve exits through a foramen, in 20–25% of patients, then an osteotomy should be performed to release the nerve. The nerve is reflected anteriorly along with the scalp flap. Dissection is continued along the orbital rim to the zygomatic process, allowing the scalp to be fully mobilized and reflected anteriorly along these bony edges. The superior and lateral aspects of the orbital rim must be well exposed as multiple osteotomies through the rim are required in order to mobilize the bone flap for the OZ approach. The superior and lateral periorbita are carefully mobilized to a depth of 1.5–2 cm. This provides space for the surgeon to perform the osteotomy without getting into the periorbita as its violation leads to significant postoperative periorbital ecchymosis. The temporalis muscle is mobilized at the superior temporal line using bovie electrocautery and a small cuff of fascia is left posteriorly, allowing for reattachment at the end of the case. The myofascial flap is reflected anteroinferiorly and retracted with fishhooks. At this stage, the superior and lateral portions of the orbital rims should be adequately exposed as well as the frontozygomatic suture as these landmarks are necessary for the next steps in the craniotomy. The details of this modified OZ craniotomy have been previously described by Balasingam et al. [2]. Please see Figs. 12.17, 12.18, and 12.19.

After the craniotomy, the bone flap is reflected anteroinferiorly; additional bony removal posteriorly along the roof of the orbit is performed. The pterion is drilled away and the dura is opened in a curvilinear fashion centered over the pterion with the base of the flap at the anterior aspect of the craniotomy. Depending on the lesion, an extradural clinoidectomy may be performed prior to opening the dura to facilitate

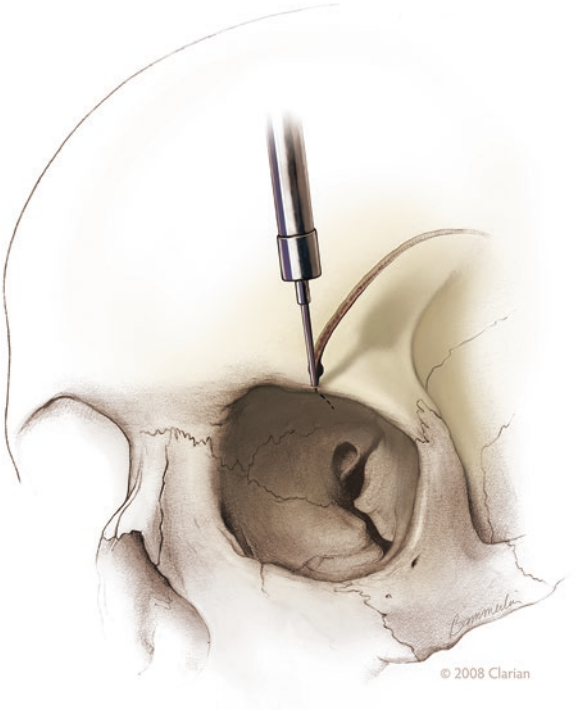


Fig. 12.17 A craniotome is used to complete a frontotemporal craniotomy from the first burr hole above the zygoma toward the orbital rim just lateral to the supraorbital foramen/notch; however, further progress of the craniotome with the footplate is stopped at the orbital roof (Used with permission from Clarian Health)

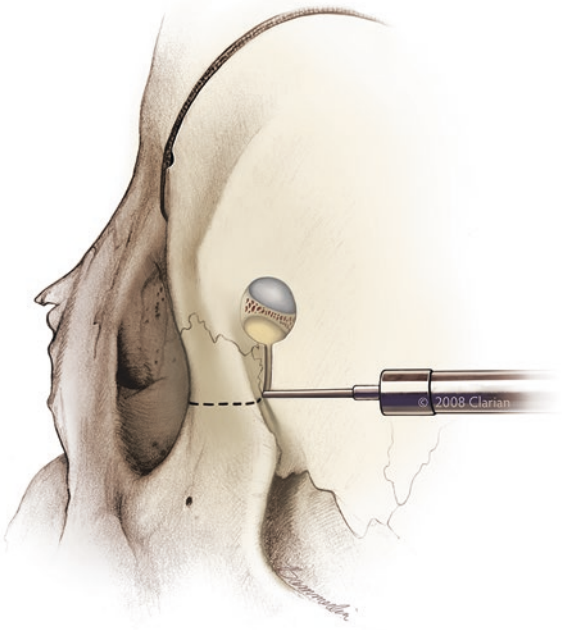


Fig. 12.18 The second orbital osteotomy involves a cut (using the B1 drill bit) from the keyhole extending inferiorly and then anteriorly below the frontozygomatic suture to disconnect the frontal process of the zygomatic bone (Used with permission from Clarian Health)

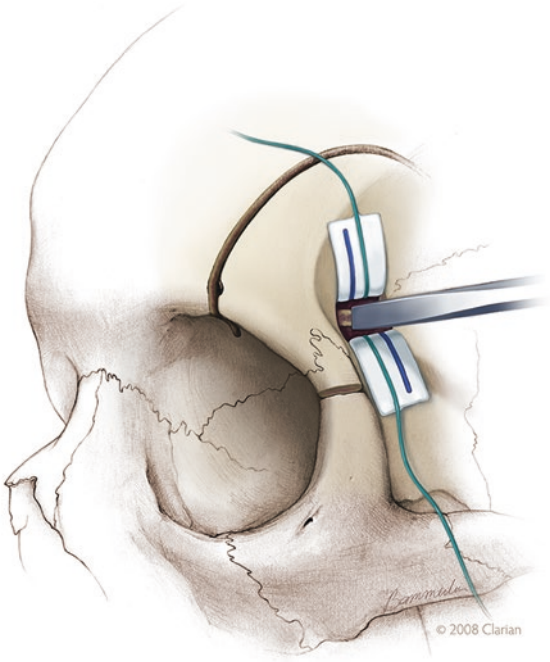


Fig. 12.19 Two cotton patties may be used to protect the frontal dura superiorly and periorbita inferiorly from the osteotome (Used with permission from Clarian Health)

increased exposure. Ideally, the dural incision should expose the sylvian fissure, superior temporal gyrus, and inferior frontal gyrus. Inferior traction along the frontal dura over the orbit using tack-up sutures gently depresses the orbital contents inferiorly and will allow for an unobstructed view along the inferior frontal lobe toward the optic chiasm. Dissection, retraction, and tumor removal may proceed as in the pterional approach. A transsylvian approach can be performed similarly to a pterional approach with a shorter working distance toward the parasellar region [10].

Complications of the OZ approach are similar to those of the pterional route, although the risk of entry into the frontal sinus and cosmetic deformity is slightly higher. Removal of the lateral wall of the orbit risks injury to the globe and removal of the orbital roof risks injury to the optic nerve. While providing superior visualization of the parasellar region and reducing frontal lobe retraction, this approach is also more time intensive and is not performed as commonly as the pterional craniotomy.

Bifrontal Approach

Most of the lesions in the parasellar space are approached through the pterional or OZ approaches. Large lesions with significant bilateral extension along the optic apparatus may be exposed using the bifrontal approach. The potential advantage of

this approach is the wide view of the optic and lamina terminalis [3]. The presence of a postfixed chiasm is another reasonable indication for this approach. However, we have rarely employed this route because the classical pterional approach is adequate to remove larger tumors. As tumor removal proceeds, the working corridor expands and additional exposure is not usually necessary.

Because the large tumors that take up a significant portion of the anterior skull are the general indication for this procedure, it is often the case that the release of CSF is difficult to achieve through cisternal dissection. As such, a lumbar drain should be placed prior to the procedure and CSF should be drained prior to opening the dura.

The scalp incision is marked out bilaterally. The incision should stay behind the hairline in both directions and must go at least the level of the pinnas bilaterally. If greater scalp mobilization is required, the incision can be extended down to the tragus. The incision is made through the galea, which is then elevated away from the pericranium using sharp dissection. The pericranium must be kept intact during this portion of the procedure as the frontal sinuses will be violated with bicoronal osteotomy and the pericranium will be necessary to cover them. An attempt is also made to preserve the main trunk of the superficial temporal arteries bilaterally by dissecting through the superficial and subcutaneous layers of the skin within the first and last 3 cm of the incision. As separation of the galea and periosteum progresses anteriorly, the supraorbital nerves are carefully preserved and elevated. An incision in the pericranium is made 5 cm superior to the supraorbital rim. A subperiosteal dissection is performed down over the frontal bone and laterally to the superior temporal lines, and a periosteal flap is reflected anteriorly while preserving the supraorbital nerves. This creates a vascularized periosteal flap for covering the frontal sinus at the end of the procedure. This flap should be retracted along with the scalp and kept moist with wet towels during the procedure.

Burr holes are placed in the keyholes on either side of the skull and a third, single burr hole is placed directly over the sagittal sinus. This burr hole should be approximately 3 cm anterior to the coronal suture. The location of this burr hole may change depending on the size of the lesion. The B1 drill bit with a footplate is used to perform osteotomy connecting the three burr holes; this makes up the posterior portion of the craniotomy. Using a craniotome, the surgeon then drills the anterior portion of the craniotomy as low and close to the orbital roof as possible. If the frontal sinus is large, a B1 bit without a footplate may be used to complete the osteotomy over the anterior and posterior walls of the frontal sinus. The bone is removed in one piece leaving the dura intact. Attention is then turned to the frontal sinus. The sinus is exenterated from its mucosa, packed with muscle or fat, and covered with Tisseel (Baxter, Deerfield, IL).

The dura is incised in a U-shape with the base along the orbital floor. This allows for the dura to be reflected along the scalp and previously mobilized pericranium. In addition, tack-up sutures may be used to aid with dural retraction. The anterior part of the sagittal sinus is ligated and coagulated along the superior edge of the craniotomy. The falx cerebri must be cut prior to mobilizing the dura.

A Greenberg retractor is affixed to the Mayfield head holder, and gentle retraction is placed on each frontal lobe as they are elevated. As previously mentioned, the anterior skull base lesions may prevent arachnoidal dissection and CSF release when using this approach; as such CSF should be drained in increments of 10–20 mL to afford more brain relaxation. The total amount of CSF should be kept to less than 60 mL. The arachnoidal cistern surrounding the olfactory bulb and tracts can be opened to allow further drainage of CSF. Sharp dissection is then performed to release the olfactory nerves from the orbital surface of the frontal lobes to the level of the olfactory trigone. During this dissection, the olfactory artery, arising lateral to the anterior cerebral artery (ACA) or collateral branches distal to the anterior communicating artery, should be preserved [7]. At the terminus of the olfactory nerve dissection, the basal interhemispheric fissure will demonstrate overhanging distal A2 segments of the anterior cerebral arteries (ACAs). The chiasmatic and lamina terminalis cisterns can be exposed with sharp dissection. The anterior communicating artery and the optic chiasm will then come into view. Incision of the lamina terminalis, which resides just posterior to the optic chiasm making up the anterior wall of the third ventricle, will provide access to the tumor behind the optic chiasm and within the third ventricle. With the tumor now in view, careful dissection from the surrounding structures with incremental debulking may be conducted until adequate tumor resection is obtained.

Following resection of the tumor, meticulous hemostasis is obtained. Copious irrigation is performed to remove any residual blood. The dura is closed in a "watertight" fashion. A Gelfoam (Braun AG, Melsungen, Germany) sponge is placed extradurally. The frontal sinus is again inspected, packed with more muscle and bone, and covered with the pericranial flap. The bone is fixated using titanium CranioFix plates (Aesculap AG, Tuttlingen, Germany). Finally, the galea is closed with interrupted sutures, and the skin is closed with staples. An optional subgaleal drain may be left in for 24 h.

This approach may be further modified to gain improved visualization of more superiorly located tumors while minimizing frontal lobe retraction. The orbital roof just medial to the supraorbital notch may be osteotomized bilaterally using a craniotome. The orbital contents should be stripped from the bone to the depth of the posterior ethmoidal artery prior to this osteotomy. A vertical cut between the crista galli and the supraorbital bar defines the posterior edge of the extended bone flap. The inferior cut is through or just superior to the frontonasal suture. At the end of the procedure, the bone can be replaced with two two-hole, low-profile titanium plates with titanium screws along the supraorbital bar.

The bicoronal approach has many potential complications and difficulties including frontal sinus entry and high risk of cosmetic deformity. The bicoronal approach also increases the risk of olfactory nerve injury with the patient being permanently anosmic postoperatively. The sacrifice of the superior sagittal sinus, although anterior to the coronal suture, may be associated with frontal lobe venous infarction. Retraction of both frontal lobes increases the risk of frontal lobe injury.

Unilateral Subfrontal

The unilateral subfrontal route is the preferred approach for lesions that extend anteriorly or laterally on one side of the skull. Traditionally, it is used for lesions located more anterior in the parasellar region, just above the pituitary gland and around the optic nerves. It has the advantage of requiring less surgical time to complete than the bicoronal approach while providing an anterior and nearly panoramic view of the sellar and parasellar lesions. The unilateral subfrontal approach may provide adequate visualization of the anterior midline lesions, as does the bilateral subfrontal approach, without the need for ligation of the superior sagittal sinus or bilateral dissection of the olfactory bulb and tract [12].

The patient is positioned supine with the head in a Mayfield head holder and rotated between 10° and 30° toward the contralateral side. As with the other approaches, the amount of head rotation should be directly correlated with the degree of lesion laterality. The head is extended approximately 30°, elevating the zygoma to the highest point. Similar to the prior unilateral approaches, the skin incision starts 1 cm anterior to the tragus and 1 cm above the zygomatic arch and extends behind the hairline to the contralateral midpupillary line. The scalp flap is elevated with sharp dissection between the galea and periosteum. The superficial fat pad is elevated with the skin flap as in the pterional approach to preserve the temporal branch of the facial nerve. Dissection is continued to the supraorbital rim and the frontozygomatic suture. The temporalis muscle is separated from the anterior aspect of the superior temporal line and the frontozygomatic process. This muscle is then retracted posteriorly [9], and the pericranium is sharply removed from the bone, preserving its pedicle anteriorly. The pericranium should be preserved in the event of frontal sinus entry. The surgical steps for dealing with sinus violation have been outlined previously.

A single burr hole is placed at the pterional keyhole. A craniotome is then used to cut along the supraorbital margin, stopping just medial to the supraorbital notch and then as far superior as dictated by preoperative imaging. The inferior edge of the craniotomy is then completed close to the level of the orbital roof. The dura is incised in a U-shaped fashion so that the base is positioned inferiorly. The dura is then tacked up with stitches.

Using the operating microscope, gentle elevation of the frontal lobe allows identification of the arachnoid attachments over the olfactory cistern, which is opened. The olfactory nerve is followed posteriorly until the anatomic windows of the subchiasmatic, opticocarotid, and retrocarotid cisterns are found. In the case of a prominent tuberculum sellae that limits visualization in the subchiasmatic space, a diamond burr drill can be used to drill down this bony structure to the level of the anterior intercavernous sinus. If necessary, the sphenoid sinus can be opened and the anterior wall of the sella turcica removed. Upon tumor visualization, either dissection away from neurovascular structures or debulking should be performed.

The complications associated with the unilateral subfrontal route are very similar to those described for the pterional craniotomy. As with the subfrontal approach, the chance of entering the frontal sinus and postoperative anosmia is greater than with the typical pterional approach.

Supraorbital Keyhole Approach

The supraorbital keyhole approach is similar to the unilateral subfrontal approach. The supraorbital approach is indicated for lesions superior to the pituitary gland and around the optic nerve. The advantages of this approach include minimal bone removal and a much smaller skin incision. However, the intracranial exposure afforded by this approach is more restrictive.

The patient's head is placed in the Mayfield head holder and turned 15–60° contralaterally such that the side of the head ipsilateral to the lesion is pointed toward the ceiling. The amount of rotation is dictated by the anatomy of the lesion based on preoperative imaging [13]. The head is extended slightly to place the malar eminence at the highest point, thereby facilitating gravitational retraction of the frontal lobe.

The eyebrow should not be shaved due to its slow regrowth. An incision is made just above the eyebrow just lateral to the supraorbital notch and follows the orbital rim laterally and inferiorly to the termination of the eyebrow. As the incision progresses medially, it should be kept more superficial to avoid injury to the supraorbital nerve and artery. The galea is then dissected away from the periosteum medially to identify and preserve the supraorbital nerve while maximizing the use and extent of the incision. The frontalis muscle is sharply dissected from the periosteum in the transverse direction and is retracted along with the superior skin flap using skin hooks. The orbicularis oculi muscle can be gently retracted inferiorly toward the orbit with retraction sutures. The pericranium is incised in a half-moon shape with a base toward the orbit for later use if the frontal sinus is violated [8]. A short anterior segment of the temporalis fascia and the muscle are released at the superior temporal line. Muscle and fascia are retracted inferolaterally to fully expose the frontozygomatic process and the keyhole.

A burr hole is placed inferior to the superior temporal line and posterior to the keyhole. A craniotomy flap similar to the unilateral subfrontal approach is then fashioned and may or may not include the lateral aspect of the orbital rim. An approximate size for this craniotomy is 10–15 mm by 15–25 mm. For further exposure, the orbital rim can be drilled down to better visualize the floor of the anterior cranial fossa (ACF) [8]. The bony ridges over the ACF floor can also be drilled down to improve exposure.

The dura is opened in a U-shaped manner with the base located inferiorly. With gentle elevation of the frontal lobe, the arachnoid cistern around the olfactory tract is visualized with the operating microscope and opened to allow for adequate CSF drainage. The frontal lobe is gently elevated and the olfactory tract is then traced back to the chiasmatic and carotid cisterns. After opening these arachnoid cisterns, the parasellar/suprasellar lesion should be within the field of view, and meticulous dissection from the surrounding structures with incremental debulking of the tumor can be conducted.

Following resection of the tumor, hemostasis is obtained, copious irrigation of the cisterns is performed, and the dura is closed with sutures. If the frontal sinus is violated, it can be addressed at this time, as described in previous sections of this

chapter. A plate of Gelfoam (Braun AG, Melsungen, Germany) is placed extradurally. The craniotomy is replaced and fixated using a burr hole cover plate. The temporalis muscle and fascia are sewn to their corresponding fascial cuffs. If the pericranial flap was not used to close the frontal sinus, it is placed back over the bone. The scalp flap is closed with galeal and subcutaneous sutures, and a topical skin glue is placed on the skin.

The main disadvantage of the supraorbital keyhole approach is that it provides a much smaller working corridor. As such, large lesions in the parasellar space are not ideal for this approach. Injury to the supraorbital nerve may cause some numbness above the eyebrow. Frontalis palsy may be a more frequent complication of this exposure than with other approaches because of the location of the incision. A spacious frontal sinus appreciated on the preoperative CT and/orMRI may be a contraindication for this form of craniotomy.

Subtemporal Approach

The subtemporal approach is infrequently used for suprasellar and parasellar lesions but may be especially useful for those lesions that extend into the infratentorial space, are retrochiasmatic, or extend into the temporal fossa [1]. This route offers the most direct approach to remove the lesions in the often "difficult to reach" retrochiasmatic space. Preoperative MR venography may be useful to assure that the vein of Labbé is not tethered anteriorly and, therefore, is not vulnerable during elevation of the temporal lobe.

It is highly advised to place a lumbar drain for CSF drainage and achieve brain relaxation to minimize temporal lobe retraction. With the patient in a supine position, the patient's head is placed in a Mayfield head holder and is rotated 60° away from the lesion and extended 30° for optimal visualization of the sella and parasellar regions [6].

A liner incision is made 1 cm anterior to the tragus, starting 1 cm below the zygomatic arch and extending 1 cm above the superior temporal line. Preservation of the superficial temporal artery is attempted as dissection down to the zygomatic arch and the temporalis fascia is performed. The periosteum is incised over the zygomatic arch and exposed subperiosteally. Anterior and posterior osteotomies at the limits of the arch are then completed, and the arch is plated for later reattachment. Following this, the temporalis muscle is dissected parallel to the line of skin incision and retracted anteriorly and posteriorly using a cerebellar retractor.

A small temporal craniotomy with an anterior burr hole is made so that the inferior bony cut is flush with the floor of the middle cranial fossa. The middle meningeal artery can be coagulated and divided where it enters the middle cranial fossa (MCF) through the foramen spinosum. A U-shaped dural flap is made with an inferior base and tacked out of the way with silk sutures. A wide, self-retaining retractor can then be inserted to gently retract the temporal lobe superiorly, providing exposure to the posterior parasellar area through the MCF. Opening of the basal cisterns along the third nerve will allow for further CSF drainage and further brain

relaxation. With the lesion now in view, dissection from the surrounding structures and incremental debulking of the tumor can proceed.

While the subtemporal approach offers a unique corridor to the retrochiasmatic tumor, it is limited by the restricted access it provides to the superior and anterior parasellar space. Postoperative difficulty in mandibular movement due to masseter and temporalis muscle dissection is frequent. In addition to common risks of craniotomies mentioned within the pterional approach, injury to the branches of the facial nerve just below the zygomatic arch is of unique concern with this approach. Significant temporal lobe retraction necessary during this surgery places the lobe at risk, and retraction injury can be especially symptomatic in the dominant hemisphere.

Final Thoughts

Transcranial removal of parasellar lesions requires proficiency in microsurgical techniques. We should not focus too much on the "exposure," but more on "what to do when we get there" in terms of handling the tumor and surrounding cerebrovascular structures. The classical pterional approach is a versatile route that allows safe exposure and removal of most parasellar lesions. The surgeon must at all times look out for the optic nerve and other adjacent cerebrovascular structures, and remain patient when handling the tumor. "Pulling" the tumor indiscriminately and cutting without scrutinizing the tips of the microscissors could be regretted later. It is better to say "here it is" and be wrong than to say "there it was" and be right.

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Endoscopic Transsphenoidal Surgery: Anatomy, Instrumentation, and Technique

13

Paolo Cappabianca, Luigi Maria Cavallo, Domenico Solari, and Alberto di Somma

Introduction

The skull base is one of the most fascinating and complex areas, from both an anatomical and a surgical standpoint; as a matter of fact, it can be involved in a variety of lesions, neoplastic and/or inflammatory and/or infectious, whose successful treatment may be troublesome, being overburdened by a high grade of invasiveness, morbidity, and mortality. A variety of innovative skull base cranio-facial approaches including anterior, antero-lateral, and postero-lateral routes have been developed over the past years [1–17]. Recently, technical advances and scientific progress have led to a progressive reduction of the invasiveness of these approaches and the possibility to access the skull base from the nose that gradually took place. The transsphenoidal approach developed perfectly fitting this conceptual way of thinking, being founded on the possibility of gaining access to the brain via a natural preconstituted path, i.e., sphenoid sinus cavity [18–22]. Initially, it has been reserved only for the surgical management of lesions involving the sellar and the closest areas up to 1987, when Weiss [23] termed and described the "extended" transsphenoidal approach, intending a transsphenoidal approach with removal of additional bone along the tuberculum sellae and the posterior planum sphenoidale to expose and access the suprasellar space [24, 25]. Later, it has been the fundamental and innovative contribution by the endoscope that boosted the extension of the transsphenoidal approach to several areas of the skull base [26–29].The endoscopic endonasal surgery has been developing through innovations and technological progress to grant the lowest rates

P. Cappabianca, MD (✉) • L.M. Cavallo, MD, PhD • D. Solari, MD, PhD • A. di Somma, MD
Division of Neurosurgery, Department of Neurosciences, Reproductive and Odontostomatological Sciences, Università degli Studi di Napoli "Federico II", Naples, Italy
e-mail: paolo.cappabianca@unina.it

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_13

of morbidity and mortality; indeed, it offers a direct approach that permits access to the suprasellar, retrosellar, and retroclival space, obviating brain retraction.

It requires specific endoscopic skills and is based on a rather different concept, since the endoscopic view that the surgeon receives on the video monitor is not the transposition of the real image, consisting of a microprocessor's elaboration. Such a brilliant intraoperative imaging modality bringing the surgeon's eyes close to the relevant target has provoked favor and disagreement, for the aspects related to the different working conditions. As a matter of fact, the endoscopic technique requires different instrumentation, consisting of different components: the endoscope, the fiberoptic cable, the light source, the camera, the monitor, and the video recording system, related one to another as a "clock mechanism." Besides, further advantages have been identified: the endoscopic endonasal technique turned out to be a less traumatic procedure, with minimal postoperative pain and better relief after surgery; in the majority of the cases, it does not require any nasal packing.

The introduction of modern endoscopic techniques afforded the renaissance of the transsphenoidal route for the treatment of several different lesions of the skull base: the endoscopic technique has been adopted according to classical indications for midline lesions and, more recently, along with surgeons' confidence, also extending them to lesions of paramedian and lateral compartments of the ventral skull base.

Endoscopic Anatomy of the Skull Base: The Endonasal Perspective

The anatomy of the midline skull base can be divided into three areas [28, 30–32]:

1. The midline anterior skull base: from the frontal sinus to the posterior ethmoidal artery
2. The middle skull base: the sphenoid sinus cavity
3. The posterior skull base: from the dorsum sellae to the cranio-vertebral junction

The Anterior Skull Base

The endonasal view of the midline anterior skull base corresponds to the roof of the nasal cavities. After the removal of the anterior and posterior ethmoid cells and of the posterior part of the nasal septum (lamina perpendicularis), the anterior skull base appears as a rectangular area limited laterally by the medial surfaces of the orbital walls (lamina papyracea), posteriorly by the planum sphenoidale and anteriorly by the two frontal recesses. Each part is formed by the lamina cribrosa medially and ethmoid labyrinth laterally [33].

The lamina cribrosa lies at the center of the anterior skull base floor; it consists of a thin osseous layer pierced by the olfactory phila: this area is enclosed between the anterior and posterior ethmoidal arteries that supply the dura mater of the ethmoidal planum, both being branches of the ophthalmic artery. These vessels send many small branches to the cribriform plate, where they anastomize with the nasal branches of the sphenopalatine artery [34–36].

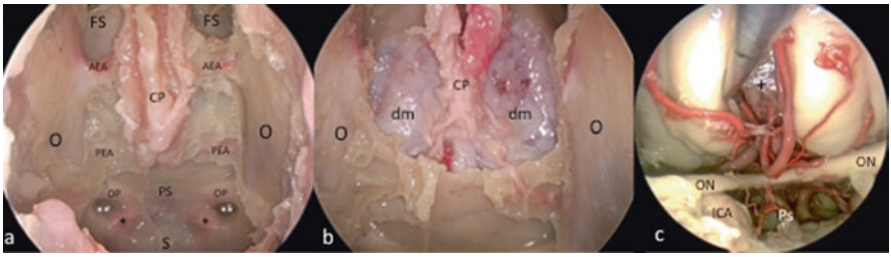

Fig. 13.1 Endoscopic endonasal view of the midline anterior skull base, enclosed between the two orbits: (**a**) the cribriform plate lies at the center of the anterior skull base floor; (**b**) after bone removal, the dura mater comes into view; (**c**) upon dural opening, an exploration of the interhemispheric cistern can be performed. *FS* frontal sinus, *AEA* anterior ethmoidal artery, *PEA* posterior ethmoidal artery, *CP* cribriform plate, *O* orbit, *PS* planum sphenoidale, *OP* optic protuberance, * carotid protuberance, ** lateral opto-carotid recess, *S* sella, *dm* dura mater, *ON* optic nerve, + arachnoid of the interhemispheric fissure, *ICA* internal carotid artery, *Ps* pituitary stalk

The superior portion of the lamina papyracea should be removed and the anterior and posterior ethmoidal arteries isolated, on both sides. The anterior skull base enclosed between the two orbits is therefore accessed: upon dural opening, the olfactory bulbs appear at the bottom of the gyri recta; with a careful retraction of the brain tissue, it is possible to expose the two frontopolar and fronto-orbital arteries with their branches, exploring the interhemispheric fissure (see Fig. 13.1).

The Middle Skull Base

The middle skull base corresponds to the posterior and lateral walls of the sphenoid sinus, where a series of protuberances and depressions are recognizable. The sellar floor is at the center, the spheno-ethmoid planum above it, and the clival indentation below; lateral to the sellar floor the bony prominences of the intracavernous carotid artery (ICA) and the optic nerve can be seen and, between them, the lateral opto-carotid recess, molded by the pneumatization of the optic strut of the anterior clinoid process [7] (see Fig. 13.2).

The superior boundary of the lateral opto-carotid recess gives attachment to the so-called ICA distal dural ring, while its inferior margin gives attachment to the thickening of the dura mater and periosteum, known as ICA proximal dural ring.

Although rarely visible in the cavity of the sphenoid sinus, it is important to define the position of the medial opto-carotid recess, since its removal on both sides significantly increases the surgical exposure over the suprasellar area. It corresponds intracranially to the medial clinoid process, which is present in about 50% of cases. The medial opto-carotid recesses can be identified using landmarks of access to the suprasellar space.

Once the sellar dura is opened, the anterior lobe of the pituitary gland comes into view and, posteriorly, the neurohypophyseal part – softer and almost gelatinous. Above, the diaphragma sellae can be seen which covers the pituitary gland, except for a small central opening in its center, transmitting the pituitary stalk. Laterally, the

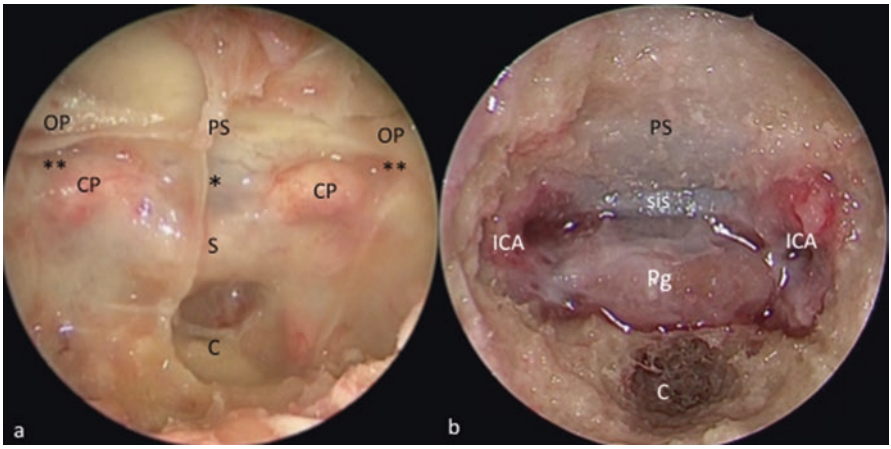

Fig. 13.2 Endoscopic endonasal view of the sphenoid sinus posterior wall. (**a**) The pituitary gland is surrounded by the internal carotid arteries, laterally and, (**b**) superiorly, the superior intercavernous sinus. *OP* optic protuberance, *CP* carotid protuberance, ** lateral opto-carotid recess, * tuberculum sellae (suprasellar notch), *S* sella, *C* clivus, *PS* planum sphenoidale, *sis* superior intercavernous sinus, *ICA* internal carotid artery, *Pg* pituitary gland

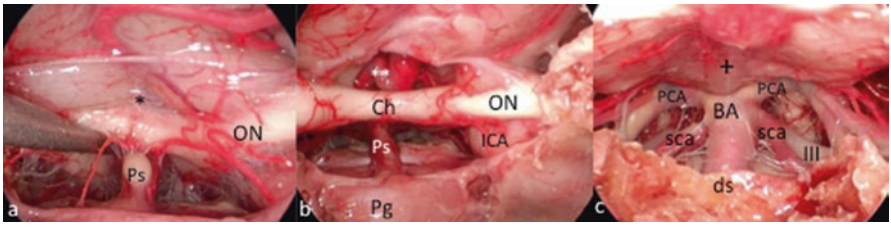

Fig. 13.3 Intradural exploration of the suprasellar areas. (**a**) The subchiasmatic suprachiasmatic, (**b**) and (**c**) retrosellar areas are shown. *Ps* pituitary stalk, * chiasmatic cistern, *ON* optic nerve, *Ch* optic chiasm, ** anterior communicating artery complex, *ICA* internal carotid artery, *Pg* pituitary gland, + tuber cinereum, *PCA* posterior cerebral artery, *sca* superior cerebellar artery, *BA* basilar artery, *III* third cranial nerve, *ds* dorsum sellae

internal carotid artery within the cavernous sinus can be appreciated at this level. Immediately above the sellar floor, the tuberculum sellae is figured out as an indent, namely the angle in between the floor itself and the sphenoid planum [37]. To explore the suprasellar region, the surgeon has to remove the bone and the dura over the sella, the tuberculum sellae, and the posterior part of the planum sphenoidale.

Once the dura has been opened, it is possible to explore the suprasellar space: it can be divided into four areas by two ideal planes, one passing through the inferior surface of the chiasm and the mammillary bodies and another passing through the posterior margin of chiasm and the dorsum sellae [38] (see Fig. 13.3).

The *subchiasmatic area* is occupied by the pituitary stalk; along the latter the superior hypophyseal arteries and the branches for the inferior surface of the optic chiasm and nerves are visible. In the *supra-chiasmatic area,* the anterior margin of the chiasm and the medial portion of the optic nerves in the chiasmatic cistern, as

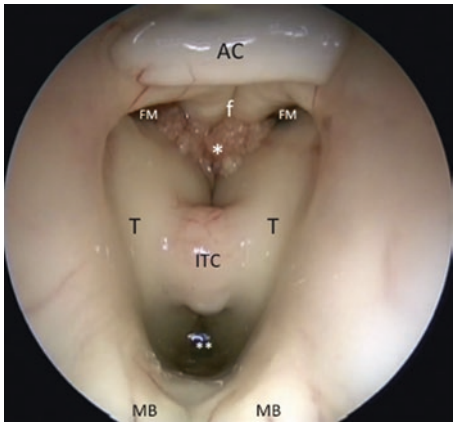

Fig. 13.4 Endoscopic endonasal view of the third ventricle chamber. The main intraventricular anatomic landmarks are depicted. *AC* anterior commissure, *FM* foramen of Monro, *MB* mammillary body, * choroid plexus, *ITC* interthalamic commissure, *f* body of fornix, *T* thalamus, ** mesencephalic area

well as the A_1 and A_2 segments and the anterior communicating artery in the lamina terminalis cistern, are visualized.

The *retrosellar area* encloses the upper third of the basilar artery, the pons, the superior cerebellar arteries, the oculomotor nerves, the posterior cerebral arteries, and lastly the mammillary bodies and the floor of the third ventricle.

The *third ventricle* is opened at the level of tuber cinereum and the ventricular cavity is accessed with a panoramic view. Besides, it can be divided by means of two ideal planes: one passing through the optic chiasm and the interthalamic commissure, and one passing through the posterior edge of the foramen of Monro and the interthalamic commissure, so that two anterior (infundibular and foraminal) and two posterior (mesencephalic and tectal) areas are defined [39] (see Fig. 13.4).

Concerning the lateral aspects of the sphenoid sinus [4], it should be said that these are represented mainly by the cavernous sinuses [3, 5, 40–42].

Various endoscopic endonasal surgical corridors have been described to get access to different areas of the cavernous sinus [38, 43], being related to the position of the intracavernous carotid artery (ICA) [26, 40, 44, 45].

The opening of the medial wall of the cavernous sinus immediately shows the C-shaped segment of the intracavernous carotid artery: at this level, the arteries to the pituitary gland arise from the internal carotid artery as the superior and inferior hypophyseal arteries, while in the upper part, the oculomotor and trochlear nerve are seen coming up from the C-shaped ICA segment toward the superior orbital fissure.

Lateral to the intracavernous carotid artery, the oculomotor, the abducent, and the maxillary nerves can be detected lying on a closer plane, as compared to that occupied by the trochlear and the ophthalmic nerves (see Fig. 13.5).

The Posterior Skull Base

The midline posterior cranial fossa as seen from the endoscopic endonasal perspective is represented by the anterior surface of the clivus, from the dorsum sellae to the cranio-vertebral junction (see Fig. 13.6). The clivus is divided by the inferior wall

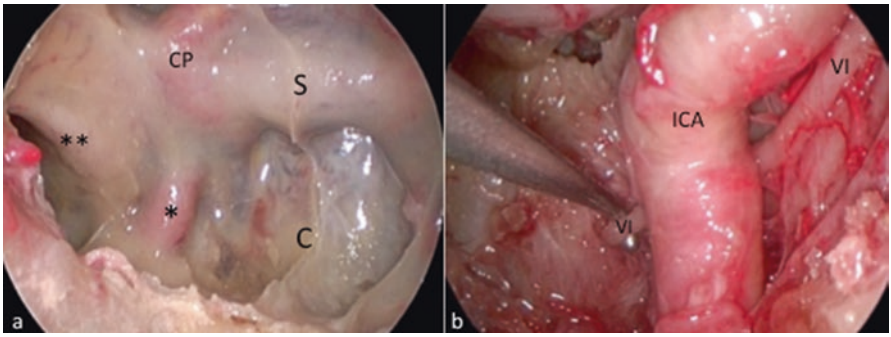

Fig. 13.5 Endoscopic endonasal route to the parasellar area. (**a**) The lateral recess of the sphenoid sinus can be seen (*right side*) and (**b**) the course of the abducent nerve can be explored (*left side*). *CP* carotid protuberance, *S* sella, *C* clivus, * carotid protuberance lateral to the clival indentation, ** bone impression of the maxillary branch of the trigeminal nerve, *VI* sixth cranial nerve, *ICA* internal carotid artery

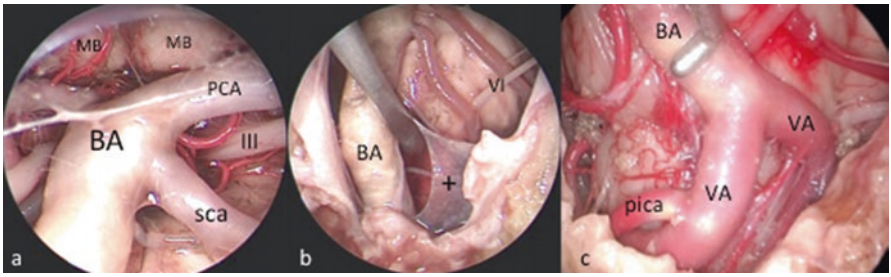

Fig. 13.6 Endoscopic endonasal exposition of the posterior skull base. The midline posterior cranial fossa as seen from the endoscopic endonasal perspective is presented (**a**) from the basilar tip, to (**b**, **c**) the vertebral arteries junction. *MB* mammillary body, *PCA* posterior cerebral artery, *sca* superior cerebellar artery, *III* third cranial nerve, *VI* sixth cranial nerve, + arachnoid of the prepontine cistern, *VA* vertebral artery, *pica* posterior inferior cerebellar artery

of the sphenoid sinus in an upper part (sphenoid portion) and in a lower part (rhinopharyngeal portion) [26, 34]. Laterally, on the sphenoid portion of the clivus, the carotid protuberances are visible. After removal of the bone of the upper part of the clivus, the periosteum-dural layer is exposed; the opening of the dura permits to visualize the basilar artery and its branches, as well as the upper cranial nerves along their courses in the posterior cranial fossa.

The rhinopharynx is exposed extending the bone removal to the inferior wall of the sphenoid sinus. The lower third of the clivus is removed and both the *foramina lacera* are identified, representing the lateral limit of the approach at this level. It is possible to further enlarge this opening by removing the anterior third of the occipital condyles, without entering the hypoglossal canal, which is located at the junction of the anterior and middle third of each occipital condyle. Moreover, the articular surface of the condyle is located on its lateral portion, so that the removal of its inner

third, through an anterior route, does not involve the articular junction [8, 30, 46]. The mucosa of the rhinopharynx is removed, and the atlanto-occipital membrane, the longus capitis and colli muscles, the atlas, and axis are exposed. The anterior arch of the atlas is removed and the odontoid is exposed. Using the microdrill, the dens is thinned; it is then separated from the apical and alar ligaments and finally dissected from the transverse ligament and removed.

The opening of the dura permits to expose all the neurovascular structures piercing the anterior part of the foramen magnum. The vertebral arteries occupy the most anterior aspect, ascending in front of the rootlets of the hypoglossal nerve to fuse into the basilar artery at the level of the medulla oblongata; two vessels branch off the vertebral artery, i.e., the posterior inferior cerebellar artery, which courses backward around the lateral surface of the medulla and between the rootlets of glossopharyngeal, vagus, and accessory nerves, and the anterior spinal artery.

The lower cranial nerves (IX-X-XI-XII) and the acoustic-facial bundle (VII-VIII) along with the anterior inferior cerebellar artery could be identified in a more deep and superior aspect of this region.

Endoscopic Endonasal Approaches

Basic Concepts

The endoscopic endonasal procedure is a two-surgeon, three-, or four-handed surgical technique requiring a duo, usually an ENT or head and neck surgeon and a neurosurgeon [26–28, 47]; the otolaryngologist performs the nasal steps of the approach and then drives the endoscope "dynamically," while the neurosurgeon performs a bimanual dissection and tumor removal.

The first surgeon is on the patient's right side, in front of him or her. The endoscopic equipment and the neuronavigation system are positioned behind the head of the patient and in front of the surgeon. Each surgeon looks into a dedicated monitor, adjusted in front of him or her at personalized height and distance.

If the surgeon is right-handed, the endoscope is placed in the superior aspect of patient's right nostril (12 o'clock) to allow suction insertion inferiorly (6 o'clock), while the main instruments will be in the left nostril; the opposite setting will be adopted in case of a left-handed surgeon.

Adequate surgical corridor [28] could be achieved by displacing laterally a middle turbinate on one side and removing the contralateral one – its mucoperichondrium graft will serve for the skull base repair – in the nostril where the endoscope will be inserted and thereafter further enlarged by means of a tailored bilateral ethmoidectomy. Bilateral middle turbinectomy could be performed if a wide orbit-to-obit foremost anterior skull base area should be accessed. A wider anterior sphenoidotomy is required, especially in lateral and superior directions where bony spurs are flattened in order to create adequate space for the endoscope during the deeper steps of the procedure. When performing refining of sphenoidotomy, care should be taken to not damage the sphenopalatine artery branches and the posterior ethmoidal arteries.

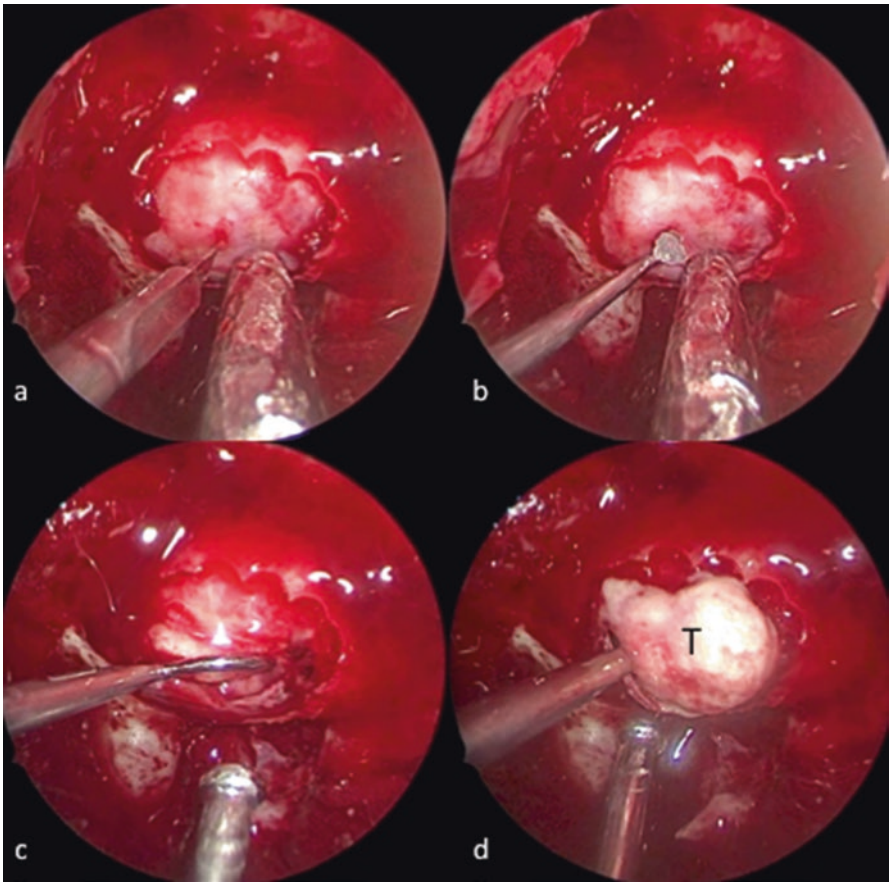

Fig. 13.7 Endoscopic endonasal removal of an intrasellar pituitary macroadenoma. (**a**) Incision of the dura mater using a telescopic blade; (**b**) enlarging of the dura mater opening; (**c, d**) extracapsular tumor removal with the aid of curette. *T* tumor

The harvesting of a vascularized nasal septal flap (Hadad-Bassagasteguy flap) [48, 49] could be performed at this point: nevertheless, we retain it is better to draw mucosa incision and then raise it off at the end of the surgical procedure [50].

As per microsurgical paradigm, bimanual dissection is performed under dynamic visual control between close-up and panoramic views [26, 50, 51] (see Figs. 13.7 and 13.8).

Surgical Instrumentation

The endoscopic endonasal procedure is performed using a rigid endoscope – 18 cm in length 4 mm in diameter without any working channel – (Karl Storz® & Co, Tuttlingen, Germany), as the sole visualizing instrument of the surgical field along the whole procedure. The direction of view could range from 0° to 120°, according to the objective; hence, the procedure is run with 0° scope, while 30° and 45° are adopted to explore the intradural cavity after lesion removal.

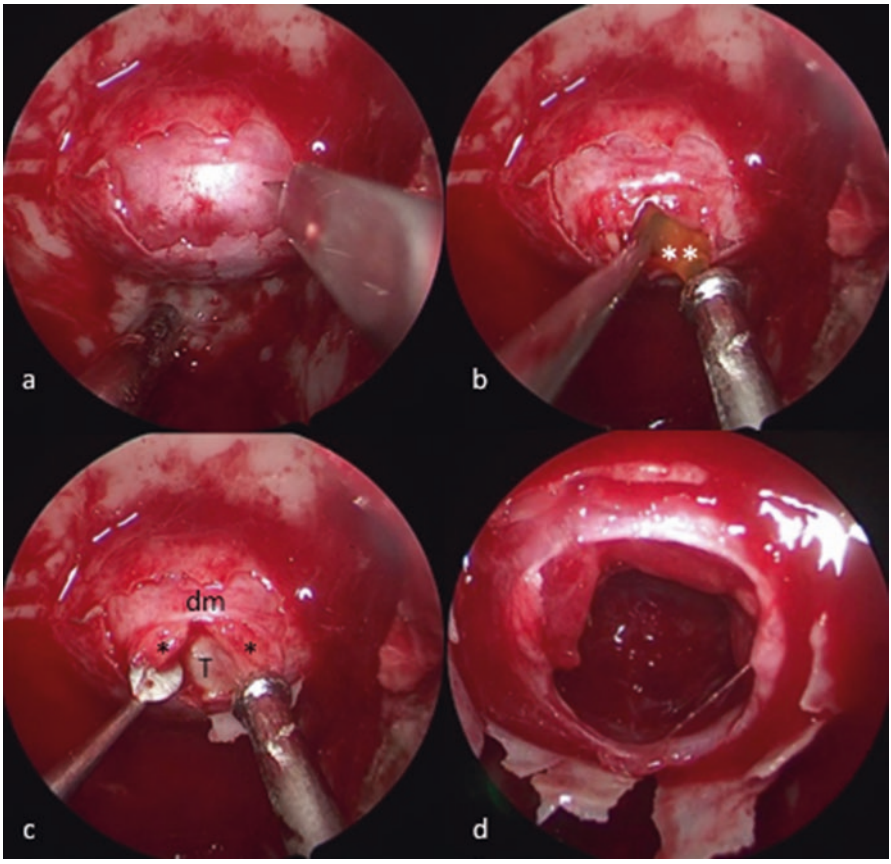

Fig. 13.8 Endoscopic endonasal removal of an infradiaphragmatic craniopharyngioma. (**a**) Incision of the dura mater; (**b**) aspiration of the "motor-oil" like fluid component; (**c**) exposure of the tumor capsule just behind the pituitary gland; (**d**) final exploration of the tumor cavity at the end of tumor removal. *T* tumor, ** motor-oil fluid, * split pituitary gland, *dm* dura mater

The endoscope consists of three main parts: a mechanical shaft, glass fiber bundles for light illumination, and optics (objective, eyepiece, relay system); it is used through a sheath connected to a cleaning-irrigation system that permits cleaning and defogging of the distal lens, without the insertion and removal of the endoscope for such purposes. The endoscope is connected to an HD camera platform (KARL STORZ IMAGE1 SPIES™ – Storz Professional Image Enhancement System, which features an innovative technology related to an improved image quality visualization system) and to a recording system.

The surgical procedure requires a detailed, complete preoperative planning, even integrated by tridimensional computerized reconstruction of MRI and/or CT scans.

Besides, an image-guided system (neuronavigator) is helpful – especially when the classic landmarks are not easily identifiable – to provide in regard to anatomy and trajectory, offering more precision in defining the bony boundaries and the neurovascular spatial relationships [26, 52–55].

Because of the different environment defined for the endoscopic technique, mostly depending on the absence of the transsphenoidal retractor, dedicated surgical instruments are needed. Instruments should thus be specifically designed to move easily and safely in a limited surgical corridor, being inserted along the same axis of the endoscope, in order to permit movements in all the visible corners of the surgical field. It should be remembered, then, that instruments must be inserted in the nasal cavity by feel and memory, unless the endoscope is removed each time apart a different instrument is used [56, 57].

Finally, it is extremely important to use further adjunctive tools: different *endonasal bipolar forceps* have been designed to consent easier introduction and maneuverability within the nasal cavity, with various diameters and lengths. *High-speed low-profile drills*, long enough but not too bulky, may be very helpful for opening the bony structures to gain access to the dural space. Finally, it is of utmost importance to use the *micro Doppler probe* to insonate the major arteries [26, 56].

Patient Positioning

The patient is placed supine or in slight Trendelenburg's position with the head turned 10–15° on the horizontal plane, toward the surgeon, fixed in a rigid three-pin Mayfield-Kees skeletal fixation device in order to allow the use of the neuronavigation systems. In the sagittal plane, the head is extended for about 10–15° to achieve a more anterior trajectory, to avoid either the endoscope or the surgical instruments hitting the thorax of the patient.

On the contrary, the head is slightly flexed to gain a more comfortable trajectory toward the posterior areas of the skull base, represented by the caudal aspect of the ventral skull base, i.e., the clival/CVJ area.

The Transtuberculum Transplanum Approach to the Suprasellar Area

After the preliminary steps for extended transsphenoidal approaches have been performed, bone removal over the sella starts with the drilling of the tuberculum sellae, which, from an inferior view, corresponds to the angle formed by the planum sphenoidale with the sellar floor. The drilling is then extended bilaterally, toward both the medial opto-carotid recesses. The extension of the bone removal depends on the size of the lesion and is performed under the control of neuronavigator. During the bone opening, it is not so rare to cause bleeding of the superior intercavernous sinus. In such cases, it is preferable to close the sinus with bipolar forceps instead of using the hemoclips, which narrows the dural opening; two horizontal incisions are made just few millimeters above and below the superior intercavernous sinus.

The dissection and the removal of the lesion in the suprasellar area follow the same principles of microsurgery and use low-profile instruments and dedicated bipolar forceps. The strategy for tumor removal is tailored to each lesion, so that it will be different for giant pituitary adenomas, craniopharyngiomas or meningiomas (see Fig. 13.9).

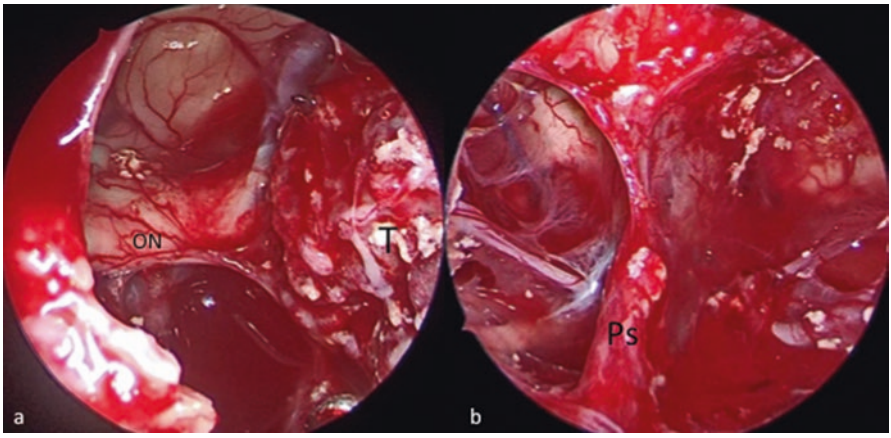

Fig. 13.9 Extended endoscopic approach to the planum sphenoidale for the removal of a supradiaphragmatic craniopharyngioma. (**a**) The adherence of the tumor to the optic nerve is shown. (**b**) At the end of tumor removal, the pituitary stalk came into view at the center of the surgical field. *T* tumor, *ON* optic nerve, *Ps* pituitary stalk

Approach to the Ethmoidal Planum

The endoscopic endonasal technique for the management of lesions of sphenoethmoidal region has become popular for CSF leaks, and subsequently for meningoencephaloceles and selected benign tumors of the anterior skull base [58–61]. More recently the collaboration among ENT surgeons and neurosurgeons has brought advances in the use of the endoscopic endonasal technique in neurosurgery, thus permitting the pure endonasal treatment of intradural lesions, such as olfactory groove meningiomas or esthesioneuroblastomas [62–69].

Usually the bone of anterior skull base enclosed between the two orbits is removed, thus creating a surgical corridor, which can be extended laterally between the two medial orbital walls and antero-posteriorly from the frontal sinus to the sella, according to lesion extension. Once again, the intradural maneuvers are performed according to conventional microsurgical principles (see Fig. 13.10).

Approaches to the Cavernous Sinus and Lateral Recess of the Sphenoid Sinus

Different endoscopic endonasal surgical corridors have been described to gain access to different areas of the cavernous sinus [41, 45, 70–75]. These corridors have been related to the position of the intracavernous carotid artery (ICA). The first approach permits access to a compartment of the cavernous sinus medial to the ICA, while a second approach allows access to a compartment lateral to the ICA.

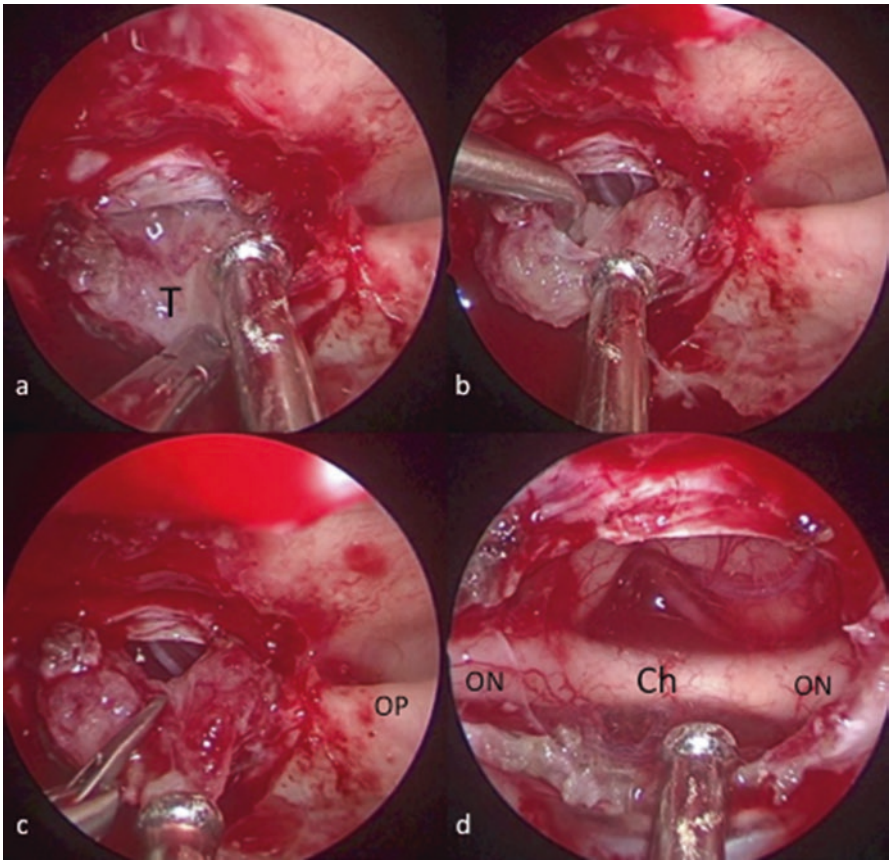

Fig. 13.10 Extended endoscopic approach to the planum sphenoidale for the removal of a tuberculum sellae meningioma. (**a**, **b**) The extracapsular dissection and (**c**) tumor debulking is shown. (**d**) The surgical cavity with the main neurovascular structures being preserved is explored. *T* tumor, *OP* optic protuberance, *ON* optic nerve, *Ch* Chiasm

Approach to the Medial Compartment of the Cavernous Sinus

Is indicated for lesions arising from the sella and projecting through the medial wall of the cavernous sinus, without extension into the lateral compartment. Actually it is mainly indicated in cases of pituitary adenomas. The procedure begins with the introduction of the endoscope through the nostril contralateral to the parasellar extension of the lesion. This is because the endoscopic approach is paramedian and the view provided by the endoscope is much wider on the contralateral side. After the removal of the intra-suprasellar portion of pituitary adenoma, the intracavernous portion of the lesion is faced. The tumor itself enlarges the C-shaped parasellar carotid artery, thus making easier the suctioning and the curettage through this corridor. The completeness of the lesion removal is confirmed by venous bleeding, easily controlled with irrigation and temporary sellar packing with hemostatic agents and/or cottonoids.

Approach to the Lateral Compartment of the Cavernous Sinus and to the Lateral Recess of the Sphenoid Sinus

Is indicated in the case of tumors involving the entire cavernous sinus and arising from the sella, such as pituitary adenomas, or lesions coming from surrounding areas (middle cranial fossa, clivus, pterygopalatine fossa), such as chordomas and chondrosarcomas. This approach is ipsilateral to the parasellar extension of the lesion. The anterior wall of the sphenoid sinus and its septa are then widely removed in order to expose all the landmarks on the posterior wall of the sphenoid sinus. The bulla ethmoidalis and the anterior and posterior ethmoid cells are removed on the same side of the parasellar extension of the lesion, to create a wide surgical corridor between the nasal septum and the lamina papyracea.

The sphenopalatine artery is then isolated with bipolar coagulation or the use of hemoclip, if necessary. At this point the medial pterygoid process is removed with the microdrill providing direct access to the lateral recess of the sphenoid sinus (LRSS) and thus to the lateral compartment of the cavernous sinus.

Once the anterior face of the lesion has been exposed, before opening the dura, the use of neuronavigation and the micro Doppler is mandatory in identifying the exact position of the ICA. Tumor removal proceeds from the extracavernous to the intracavernous portion. The dura is then opened as far as possible from the ICA, which, in case of pituitary adenomas, allows the lesion to emerge under pressure. Delicate maneuvers of curettage and suction usually allow the removal of the parasellar portion of the lesion, in the same fashion as for the intrasellar portion. Only after the removal has been completed will some bleeding begin, which is usually easily controlled with the use of hemostatic agents.

Approach to the Clivus, Cranio-vertebral Junction, and Anterior Portion of the Foramen Magnum

The endoscope through the nose has been used for the management of clival lesions and more recently also for lesions located at the CVJ, either extradural or intradural [76–82]. The endoscopic endonasal approach provides the same advantages of direct route and minimal neurovascular manipulation offered by the transoral approach, but with a wider and closer view. Furthermore, it avoids some of the disadvantages related to the transoral approach, such as the need for mouth retractors and splitting of the soft palate.

Access to the clivus needs a lower trajectory in respect to that necessary for the sellar region. After the preliminary steps (middle turbinectomy, removal of the posterior part of the nasal septum, wide sphenoidotomy), the procedure goes on with the removal of the inferior wall of the sphenoid sinus up to identifying the Vidian nerves that represent the lateral limits of the surgical corridor. The vomer and the inferior wall of the sphenoid sinus are completely removed, preserving the mucosa covering these structures, in order to create a useful mucosal flap for the closure of the surgical field. The bone of the clivus, in accordance with the surgical necessity, is drilled and removed. At the level of the sphenoidal portion of the clivus, the

approach is limited laterally by the bony protuberances of intracavernous carotid artery. Furthermore, it is important to highlight that the abducens nerve enters the cavernous sinus by passing through the basilar sinus medially than the paraclival tract of the intracavernous carotid artery. In case of lower extension of the lesion, it is possible to extend downward the bone removal up to the C2 vertebral body.

Reconstruction Techniques

Due to the consistent intraoperative CSF leakage resulting from a wider dural opening, an accurate reconstruction of the skull base defect becomes mandatory after lesion removal. The reconstruction should be watertight to prevent postoperative CSF leak, which could occur especially if lesion removal has required a large opening of the arachnoid cisterns or of the third ventricle and/or Liliequist membrane (see Fig. 13.11).

It is mandatory to perform the reconstruction according to Kelly's scale, for Grade 3 leakage [83] in the attempt to obtain (i) intradural sealing of the arachnoid; (ii) resilient closure of the osteo-dural defect; (iii) stability and integration of the materials.

Usually, a thin layer of fat and fibrin glue (Tisseel®, Baxter, Vienna, Austria), a piece of abdominal fat or both are positioned in the intradural space to fill the post-surgical cavity and act as first barrier to CSF. Thereafter, the closure of the osteo-dural defect is achieved mainly as per two different strategies: (i) the so-called gasket seal or grandma's cap technique, in which a single layer of the dural substitute is positioned in the extradural space [84, 85] with a tailored foil of resorbable semi-solid material overlapped in order to fix the first one in the extradural space; (ii) in the "sandwich" technique, three-layer foil of dural substitute with the fat sutured to its inner aspect is placed both intradurally (the fat and two layers) and extradurally (the outer sheath of dural substitute). Vascularized Hadad pedicled flap [48, 49] and, eventually, free mucoperichondrium flap are then placed over the posterior wall of the sphenoid sinus. Fibrin glue and oxidized cellulose are used to ease adherence of mucosa flap over bony surface and hold the material in place.

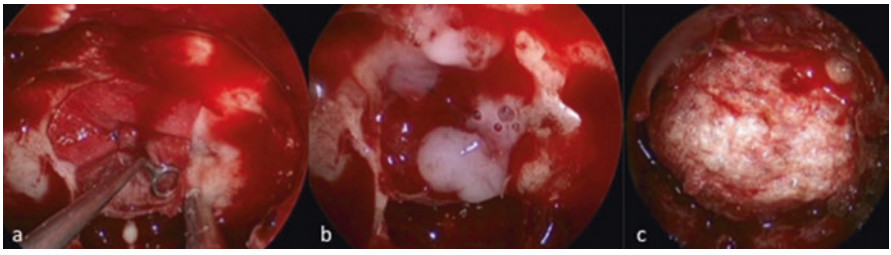

Fig. 13.11 The skull base defect is reconstructed using (**a**) multilayer dural substitute foil, (**b**) reinforced with fibrin glue and (**c**) fibrin sealant patch in the extradural space

Conclusions

The endoscope has opened the eyes of the surgeon to structures such as the planum sphenoidale, the clivus, the carotid, and optic bony protuberances, from an upside-down view compared with the common top-down surgical view. Thus, pathologies arising or extending in these regions – once approachable only with more invasive transcranial surgery – such as craniopharyngiomas, tuberculum sellae meningiomas, macroadenomas involving the cavernous sinus, upper clival chordomas, can be removed via the endonasal route. The endoscopic endonasal approach is increasing in popularity every day, thanks to the interest of patients, cooperating surgeons from different specialties, and technologic investors. Through the last two decades, an interesting interchange between the evolving approaches and the new technological advances has taken place.

Although at a first glance it might be considered something that everyone can do, this surgery requires advanced and specialized training, both in the lab, with ad hoc anatomical dissections, and in the operating room; one should become familiar with endoscopic skills, endoscopic anatomy, and complication avoidance and management.

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Three-Dimensional Endoscopy for Skull Base Surgery

14

Jason K. Chu, Brandon A. Miller, and Nelson M. Oyesiku

Introduction

The transsphenoidal approach (TSA) remains the method of choice for resection of pituitary adenomas and the endoscope has advanced pituitary surgery, replacing microscopy as the preferred technique in experienced hands [1]. This approach is associated with a relatively small number of complications, with transient diabetes insipidus being the most common, occurring in less than 5% of patients [2]. Although endoscopic transsphenoidal procedures are most often performed for resection of pituitary adenomas, the indications for transsphenoidal surgery have expanded with the development of extended approaches that involve the anterior skull base (tuberculum sellae and planum sphenoidale), suprasellar area, third ventricle, cavernous sinus, clivus, ventral brainstem, and craniocervical junction. For example, extended approaches allow access to skull base lesions such as tuberculum sellae and planum sphenoidale meningiomas, as well as large sellar/suprasellar masses that previously required a transcranial approach. Extended transsphenoidal approaches have also improved the ability to access the cavernous sinus, and studies have demonstrated the efficacy of this approach for adenomas invading the cavernous sinus [3]. However, these extended approaches increase the rate of complications [4] as they require additional bony and dural exposure along the skull base and intradural intervention. Additionally, a deep appreciation of the surgical anatomy from this inverted vantage is paramount for complication avoidance, especially when working in close proximity to critical neurovascular structures in the suprasellar cisterns or the ventral brainstem.

The development of three-dimensional (3D) endoscopy systems has introduced a new dimension for endoscopic transsphenoidal skull base surgery. These systems address the main limitation of current 2D endoscopes by combining the direct

J.K. Chu, MD, MSc • B.A. Miller, MD, PhD • N.M. Oyesiku, MD, PhD, FACS (✉)
Department of Neurosurgery, Emory University, Atlanta, GA, USA
e-mail: noyesik@emory.edu

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_14

illumination and wide surgical view seen in endoscopy and the depth of field and stereopsis provided by microscopy, resulting in superior visualization of the surrounding sellar anatomy and pathology free of "fish-eye" distortion and the need to accommodate for the loss of stereopsis. While data regarding the advantages of new 3D over 2D systems is still evolving, early studies evaluating the safety and effectiveness of these systems have shown excellent results [5–7]. We expect that as 3D endoscopy technology continues to improve and the endonasal approach gains more favor with neurosurgeons at more institutions, 3D endoscopic transsphenoidal surgery will become the new standard for most pituitary, parasellar, and anterior skull base lesions.

Historical Developments in Endoscopic Transsphenoidal Surgery

Transsphenoidal surgery for a lesion of the pituitary gland was first performed by Schloffer in 1907 [8]. Harvey Cushing performed his first transsphenoidal operation in 1909 with the successful treatment of a patient with acromegaly [9]. However, the transsphenoidal approach remained out of favor in the neurosurgical community at large until the development and deployment of the operating microscope. Hardy was the first to perform a selective microadenectomy in 1962 using a microscopic transsphenoidal approach [10]. Dott, Guiot, and Hardy championed the procedure during the 1960s and established the microscopic transsphenoidal approach as the preferred method for surgical resection of pituitary adenomas [8]. A resurgence of endoscopy in surgery occurred during the 1970s and, from a neurosurgery standpoint, was initially used as an adjunct to microscopy for transsphenoidal surgeries. It was not until the 1990s that the first "purely" endoscopic transsphenoidal approaches were popularized by Jankowski, Sethi and Pillay, Jho, Carru, Cappabianca, and others [11]. Over the last 20 years, technological advancements have further developed smaller sized endoscopes with high definition (HD). The latest innovation is the incorporation of 3D technology into endoscopic surgery.

Technical Basis of Three-Dimensional Endoscopy

Stereoscopic vision requires binocular vision, where the left and right eye view a slightly displaced image of an object (Fig. 14.1). The differences seen through each eye are processed by the visual system and such disparities generate a sense of depth [12]. As binocular vision is required for this phenomenon, previous single-lens endoscopes have been unable to generate a 3D image.

Early 3D endoscopy attempted to recreate human stereoscopy with the use of a dual-channel system. These systems utilize two cameras to deliver two slightly different images to the surgeon. While simple, this system required a cumbersome large scope-camera complex. Moreover, the use of two different cameras can create disparities in color, image quality, and brightness that often resulted in untoward side effects, including headache, dizziness, and eye strain. Other attempts to replicate 3D vision have included a "dual chip-on-the tip," where two video tips are mounted

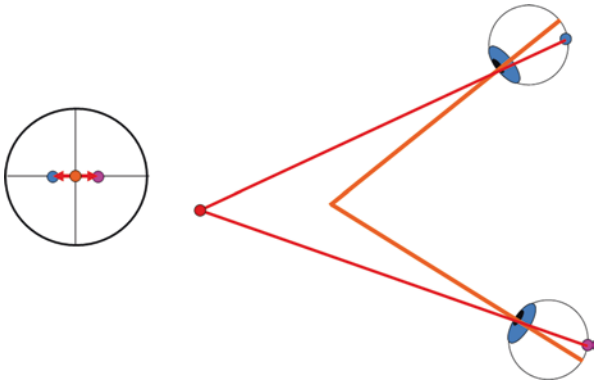

Fig. 14.1 Binocular vision is required for stereopsis. The perceived differences seen through each eye are processed, leading to depth perception (From http://www.visionsense.com/)

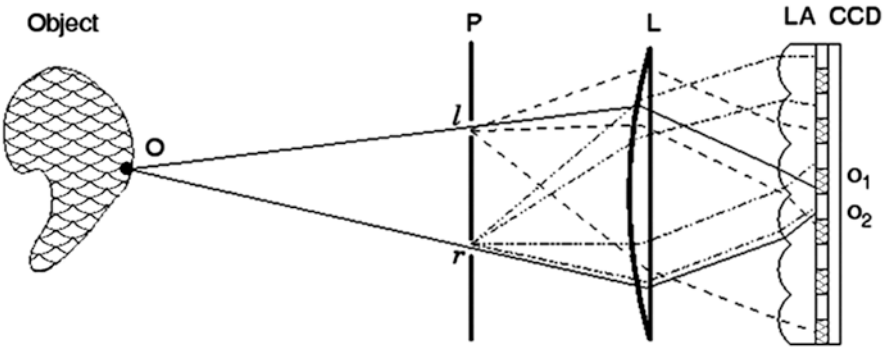

Fig. 14.2 The Visionsense (New York, NY) "insect eye" technology. Light from an object (*O*) passes through a dual-pupil imaging objective (*P*) and split left (*l*) and right (*r*). Light is then focused through a lens (*L*) onto a lenticular microarray of lenses (*LA*) in front of a charged coupled device (*CCD*) microchip. Therefore, light from the object is generated twice (O_1, left; O_2, right) and the distance between O_1 and O_2 represents the disparity between the left and right views of the object. The microchip processes these images to generate stereoscopic vision for the user (From Tabaee et al. [14])

at the end of an endoscope, as well as a "shutter" mechanism, a technique that relies on the fact that the camera is in constant motion and a single image can be divided by a shutter into two different images with minor angle changes. However, both of these technologies have been unable to create a reliably convincing 3D effect [13].

The most recent advancement in 3D endoscopy has been the introduction of "insect eye" technology patented by Visionsense (New York, NY) [13]. In these systems, a 3D image is created with the assistance of a dual-pupil imaging objective placed in front of a microarray of lenses at the end of the endoscope. First, the dual-pupil imaging objective is able to filter images into both the left and right eye channels. The images are then focused onto an image sensor made up of a microarray of lenses, similar to the compound eye of an insect, which then processes the data and digitally reconstructs a three-dimensional picture (Fig. 14.2). Images from the left

and right channels are projected onto a single liquid crystal display (LCD) and the viewer wears polarized 3D glasses to filter the left and right channels into their respective eyes. With this technique, stereoscopy is preserved and provides the viewer with the advantage of accurate depth perception and minimal side effects.

The Visionsense 3D system has been approved by the US Food and Drug Administration, as well as by CE in Europe. The latest iteration of the Visionsense system (VSIII System) was introduced in 2014. The endoscope contains a 3.3 mm digital "insect eye" sensor inside a 4 mm scope (interpupillary distance 0.8 mm). An alternative 5.5 mm outer diameter scope is also available. Images are displayed in high definition, 1080p resolution (1920×1080 pixels). The endoscope is available in both 0º and 30º angles, and can provide a field of view 75º or 105º with a depth of field between 15 and 70 mm. There is an inherent autofocus system within the endoscope that provides consistent image quality during the procedure. Endoscope length is also customizable to meet the surgeon's needs. Images are displayed onto any size LED monitor and the viewer wears lightweight, polarized glasses to effect stereoscopic vision (Fig. 14.3). In comparison to the previous iteration of the Visionsense machine (VSII), the new unit provides a smaller and more ergonomic endoscope, higher resolution image (SD vs HD, Fig. 14.4), and a streamlined Visionsense console control unit.

Advantages of Three-Dimensional Visualization

Proper visualization of anatomy is one of the most important factors in optimizing hand-eye coordination, surgeon's performance, and ipso facto reducing intraoperative complications. For example, a systematic study of intraoperative bile duct injuries in laparoscopic surgery showed 97% of injuries to be due to visual perception errors [15]. Faults in technical skill were present in only 3% of injuries. Therefore, it stands to reason that a system providing the surgeon with a superior visual image ipso facto reduces the risk of surgery.

When dealing with 2D endoscopic views, the main visual limitations are loss of depth perception, fish-eye image distortion, difficulty with hand-eye coordination, and impaired ability to estimate size and distance [5]. An estimate of depth perception is typically obtained with motion parallax, where moving the endoscope provides cues as to depth perception. These problems have long been recognized, and 3D endoscopes were first introduced with the goal of simulating depth perception approaching that of microscopy and enhancing surgical visualization. This is especially important for skull base surgeons that rely on accurately identifying anatomical landmarks, their shape, size and their canonical relationships and distance to other equally important structures.

Several studies have demonstrated that users of 3D endoscopy have improved speed, accuracy, and reduced error rate compared to their 2D counterparts [6, 7, 14, 16, 17]. When asked to complete a series of simulated task-paradigms in 2D and 3D, one study found that fewer task errors were made and task efficiency was increased when utilizing the 3D endoscope. Overall, 75% of participants favored

Fig. 14.3 The latest iteration of the Visionsense system: the VSIII endoscope (**a**) and console control unit (**b**) that is made up of a 24″ LED display, a computer, and the endoscope interface (From http://www.visionsense.com/)

the 3D endoscope and 87.5% felt that 3D visualization assisted their ability to complete the assigned tasks [6]. A study by Taffinder and colleagues showed that 3D endoscopy improves the performance of both experienced and novice surgeons, and even closed the gap between the two groups when comparing the performance

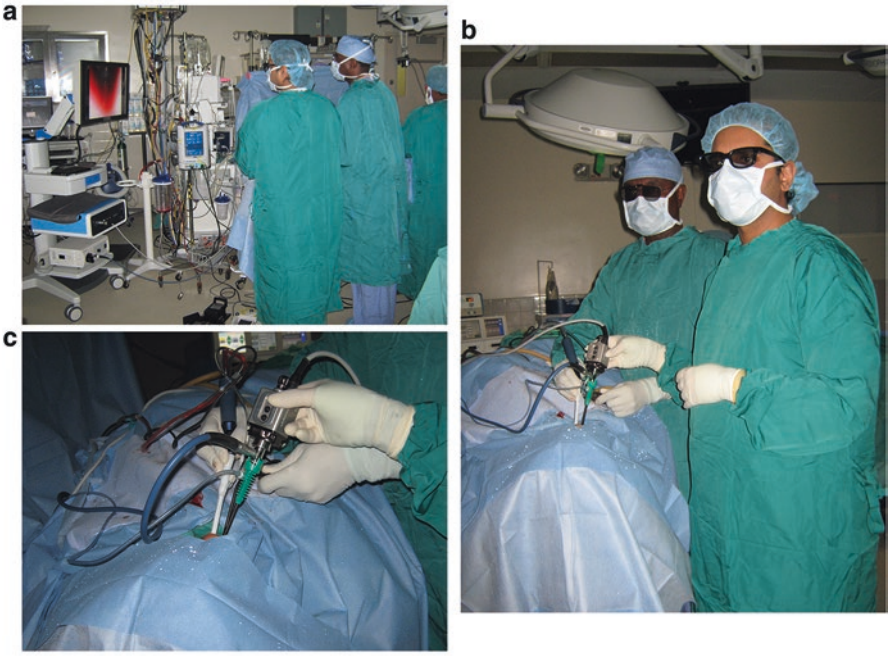

Fig. 14.4 Example of the Visionsense VSIII in the operating room (**a**). The two surgeons are wearing polarized glasses for stereoscopic vision (**b**). A close-up of the VSIII endoscope in use (**c**). The endoscope is held by an assistant and is a lightweight, ergonomic unit while the primary surgeon is free to perform bimanual dissection

of experienced surgeons using 2D imaging with the performance of novices using 3D imaging systems [18]. Similarly, there is data to suggest that the overall learning curve associated with 3D endoscopy is shorter than with 2D systems and users become acclimated with operative technique quicker in 3D [16]. This was particularly evident among younger trainees who developed proficiency within their first five procedures when using 3D visualization. In comparison, obtaining surgical confidence with 2D endoscopy has been suggested to take between 17 and 50 procedures [16]. The authors of this study believe that the clear advantages of the 3D endoscopic system outweigh the inconvenience of learning a new skill set. Therefore, 3D endoscopy has an unparalleled education benefit, by enabling the trainee to focus on understanding complex 3D anatomical relationships and perfecting surgical technique, while not being burdened by the limitations of 2D technology.

The benefit of 3D visualization appears to be accentuated with more complicated surgical tasks [19]. This is particularly true for dissection and handling of critical neurovascular structures, such as in the suprasellar or ventral brainstem region. One study suggested that 3D endoscopy can achieve the same microsurgical precision as microscopy in proper hands [20].

Despite the recent development of 2D HD endoscopes, several clinical studies have not demonstrated any significant differences in OR time, complication rate,

or hospital length of stay utilizing the 2D HD scope, even when compared to the previous generation and standard definition Visionsense VSII machine [7, 21]. It is undeniable that HD endoscopy results in better appreciation of detail, improved identification of anatomical structures, and superior distinction between pathology and normal anatomy [22]. Thus, the introduction of the 3D HD Visionsense VSIII machine represents the next evolution in 3D neuroendoscopy (Fig. 14.5). There is good reason to believe that as 3D technology continues to improve, with higher quality images (4 K resolution, 4096 × 2160 pixels) and more versatile equipment, the benefits realized by these systems will continue to grow [18].

Disadvantages of Three-Dimensional Visualization

Drawbacks of current 3D systems include minor occasional complaints in a few individuals of nausea, headaches, or eye fatigue when viewing 3D images for prolonged periods, non-HD images, a smaller endoscopic field of view, higher cost, the need for the surgeon to wear 3D glasses (although we have not found this to be an inconvenience at our institution), and red-color saturation on the displayed image [5].

In comparison to current 2D HD scopes, the 3D scopes do carry a field of view reduction of approximately 55% [23]. This is an important reminder for surgeons that toggle back and forth between the 2D and 3D endoscopes for their operations. It should be noted that this study was conducted with the Visionsense VSII machine and the newer Visionsense VSIII endoscopes not only provide a 105° field of view, but also have the ability to convert between 2D and 3D images in real time, without the need to change the endoscope and viewing tower. This can preserve the operative field of view for the duration of the case.

With the current Visionsense VSIII system (and with the Visionsense VSII system), there have been no complaints of nausea, headaches, or eye fatigue that have been described with older systems [5]. Our experience is consistent with previously reported data and we have not seen a difference between 2D and 3D endoscopy in estimated blood loss, length of hospital stay, operative time, or complications [5]. Future studies examining extent of resection, tissue discrimination, and other clinical endpoints may show greater differences between the two systems.

Implementation of Three-Dimensional Endoscopy in Transsphenoidal Surgery

With the introduction of 3D endoscopy, there have been several studies examining the safety and efficacy of its use in transsphenoidal surgery. Initially, contemporary 3D endoscopes without angled lenses were used in conjunction with 2D endoscopes that offered angled lenses [24]. Initial impressions from this early study were positive, with improved depth perception and no increase in operative time or surgical complications [24]. Another early report from the same group showed no increase in

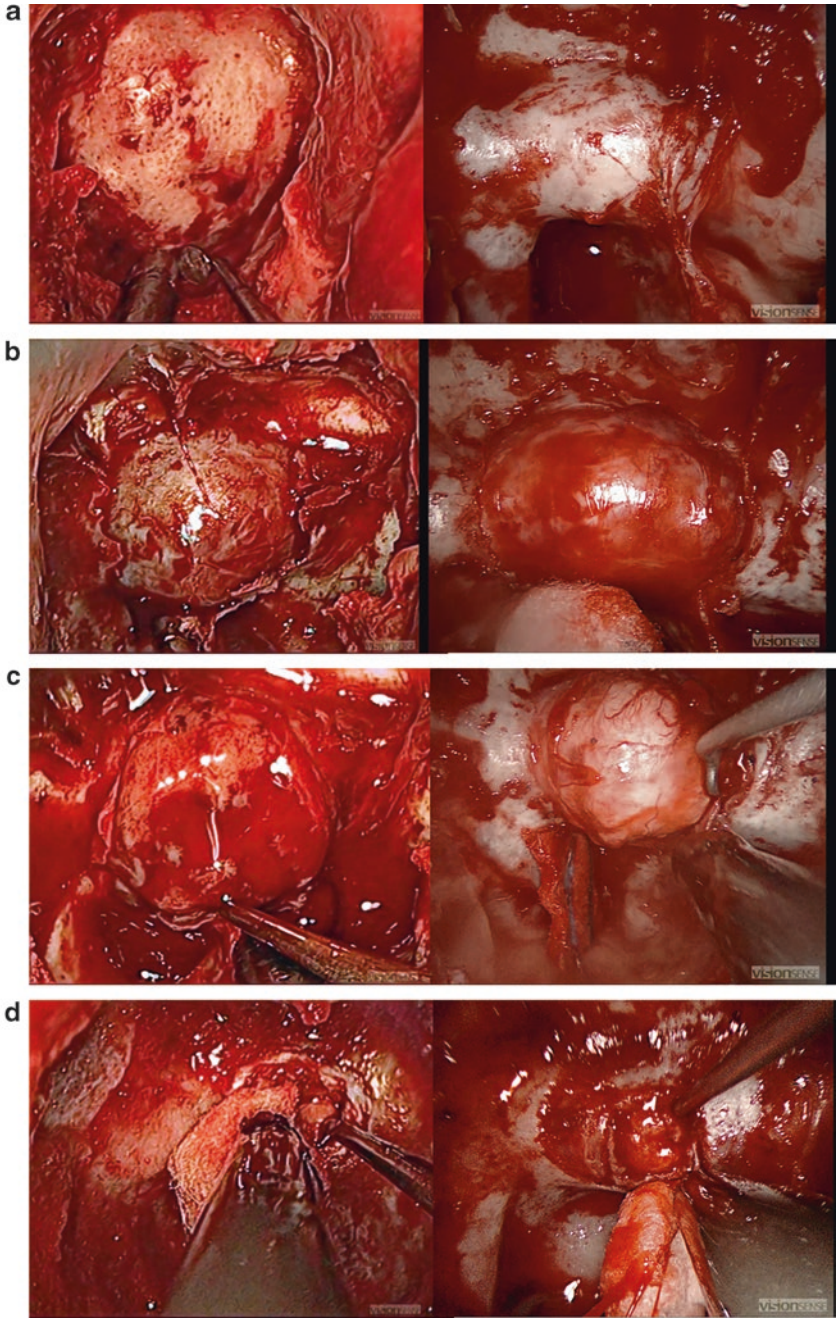

Fig. 14.5 A comparison of the Visionsense VSII (standard definition, images on the *left*) and VSIII (high definition, images on the *right*) machines. The sellar floor prior to bone removal (**a**) and exposure of the dura (**b**). Examples of a pituitary macroadenoma (**c**) and a microadenoma (**d**). The improvement in image quality from SD to HD allows for greater appreciation of the surgical anatomy and enhanced distinction of pathology. Original images were captured in 3D but were converted to 2D for publication purposes

operative complications with the deployment of a 3D system [14]. This study also reported improvement in surgeons' subjective depth perception with use of the 3D endoscope. Other recent studies from this group have found both a subjective improvement in image visualization and improved performance in efficiency in surgical tasks with the use of 3D endoscopy [6].

Recently, a systematic review of the literature was conducted by Zaidi et al. and identified only 26 published articles focused on 3D endoscopic endonasal skull base surgery [25]. Interestingly, only 14 of these 26 articles were clinically oriented, while the remaining involved simulated or cadaveric environments. All but one study reported the use of a standard definition (SD) Visionsense machine for 3D endoscopy. The results of review highlight the growing interest in 3D neuroendoscopy as there was only one publication on this topic in 2008, while a total of 14 articles were published in 2013 and 2014. Secondly, several reports suggested no significant differences in clinical outcome between 2D and 3D endoscopy. Although there was insufficient evidence to suggest clinical superiority of one modality over the other, the majority of the current literature supports the use of 3D endoscopy.

One of the earliest clinical articles to discuss 3D transsphenoidal surgery was published in 2009 [14]. This pioneering paper treated 13 patients with sellar pathology and prospectively followed them for complications (hemorrhage, cerebrospinal fluid leak, changes in visual acuity and visual fields) as well as extent of resection. The results were compared to 13 age-matched controls that were treated with a 2D scope. The authors found no differences in operative times, extent of resection, or length of hospitalization between the two groups. Subjectively, they also reported "a more natural feeling" during surgery due to the improved depth of field.

One of the largest clinical studies comparing 2D HD endoscopes (Karl Storz Neuroendoscopy) to a 3D scope (Visionsense VSII) retrospectively analyzed the results of 160 operations over a 2-year period [7]. This study reported a significantly shorter pituitary adenoma resection time utilizing the 3D scope, with a time saving of approximately 30 min over 2D endoscopy. Their data also showed that novice endoscopy users became accustomed to operating with the 3D scope quicker than the 2D scope and suggested that the 3D scope offers less of a learning curve with spatial awareness, instrument placement, and microdissection. Similar to previous data, there was not a significant difference in intraoperative cerebrospinal fluid leak rate, complication rate, or hospital course between the 2D and 3D procedures. Overall, this report demonstrated that 3D endoscopy is a safe and viable alternative for transsphenoidal surgery.

The infancy of 3D HD technology is reflected in the paucity of literature on this topic. One preclinical study compared 2D vs 3D and SD vs HD endoscopy in a randomized crossover study [26]. Naïve neuroendoscopic surgeons were placed in a simulated environment and task completion and accuracy were assessed for 2D vs 3D and SD vs HD endoscopy. The authors found that 3D allowed users to complete tasks significantly quicker than 2D, and HD images enabled improved accuracy compared to SD. The authors suggested that 3D and HD have differing but complementary effects and neither 3D nor HD alone could compensate for the other.

They provide strong evidence for the use of 3D HD endoscopes in the clinical setting. Nassimizadeh et al. were the first to report 3D HD use in a single patient and the author's noted image quality was comparable to conventional 2D HD endoscopy [21]. Moreover, they noted that the improvement in image resolution addressed one of the main drawbacks of previous 3D endoscopy systems.

Senior Author's Experience

As one of the leading Pituitary Centers of Excellence in the United States, we have transitioned to 3D endoscopy for the neurosurgical portion of all of our transsphenoidal surgeries. We also favor the use of the Visionsense VSIII and this 3D HD system has been in use since early 2014. Our experience with the VSIII has been extremely positive and parallels the current literature with better appreciation of the anatomical relationships, enhanced visualization of pathology, and an easier learning curve among neurosurgical trainees. Within our first 3 months with the Visionsense VSIII, we had conducted approximately 40 transsphenoidal surgeries. When compared to a previous report from our institution utilizing the Visionsense VSII machine, our early results suggest an improvement in operative time (mean OR time 93.4 vs 146.5 min; data not published) and lower rates of intraoperative CSF leak (4.9% vs 23%) without any difference in post-operative complications. As our data continues to be collected and analyzed, we expect further advantages of the 3D HD system will emerge. Still unsolved, but currently undergoing improvement is the matter of red saturation of the image.

Conclusions

Just as Cushing abandoned the transsphenoidal approach due to improvements in transcranial instrumentation, the quality of surgical instrumentation strongly influences today's neurosurgeons. Endoscopic transsphenoidal surgery has emerged as an important technique in pituitary surgery. As technology continues to develop, the effectiveness of 3D endoscopy will undoubtedly improve in tandem. Several studies have established that endoscopic pituitary surgery is as safe as microscopic surgery, and many experienced surgeons have transitioned to 3D HD systems based on subjective assessments of image quality and depth perception. The advantages of 3D HD endoscopy are important and consequential, including stereopsis, superior visualization, and an improved learning curve. The latter point is especially important for trainees to enhance their understanding of the anatomical relationships and gain confidence in surgical technique. As technology continues to improve and 3D systems are adopted at more institutions, 3D endoscopy will likely become the new standard of care for pituitary surgery.

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Endoscopic Transsphenoidal Pituitary Surgery: Results and Complications

15

Harminder Singh, Walid I. Essayed, Ibrahim Hussain, Kryscilla Yang, Vijay K. Anand, and Theodore H. Schwartz

Introduction

Endoscopic transsphenoidal pituitary surgery (ETPS) is rapidly replacing both the open transcranial as well as the transsphenoidal microscope-based techniques for resection of pituitary adenomas. This change has resulted from technological advances in lens and camera resolution, minimally invasive surgical instrumentation, and neuronavigation systems, leading to an improved field of view as well as more extensive approaches to skull-base lesions accessed through small portals [46]. Angled endoscopes provide visualization of recesses inside the sella and direct visualization of the medial wall of the cavernous sinus, not accessible by the operating microscope. ETPS is also less invasive, with less postoperative pain, shorter hospitalization, and fewer postoperative complications than microscopic transsphenoidal surgery [40]. The disadvantages include lack of depth perception, the need for an assistant or endoscope holder, and increased incidence of postoperative epistaxis.

Harminder Singh and Walid I. Essayed have contributed equally to this work.

H. Singh, MD
Department of Neurosurgery, Stanford University Medical Center, Stanford, CA, USA

W.I. Essayed, MD
Department of Neurosurgery, Brigham and Women's Hospital, Boston, MA, USA

I. Hussain • T.H. Schwartz (✉)
Department of Neurosurgery, Weill Cornell Medical College,
New York Presbyterian Hospital, New York, NY, USA
e-mail: schwarh@med.cornell.edu

K. Yang, MD
Baystate Health, Springfield, MA, USA

V.K. Anand, MD, FACS
Department of Otolaryngology and Head and Neck Surgery, Weill Cornell Medical College,
The New York Presbyterian Hospital-Weill Cornell Medical Center, New York, NY, USA
e-mail: vijayanandmd@aol.com

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_15

There is also a steep learning curve, requiring an average of 25–50 operations to learn the techniques necessary to operate using the endoscope [11]. Most neurosurgeons typically work with an otorhinolaryngologist, which can also limit efficiency relating to scheduling challenges. Despite this, experiences with ETPS have largely been positive, with benefits outweighing the costs.

In this chapter, we look at the surgical outcomes of functional and nonfunctional pituitary adenomas and further discuss complications associated with ETPS in general.

Nonfunctional Adenomas

Nonfunctional adenomas are by definition pituitary tumors that do not produce hormones. Their biologic latency makes them usually diagnosed at the stage of macro (>1 cm) and giant (>4 cm) adenomas. Their presence is revealed by symptoms related to mass effect on the pituitary gland and the surrounding structures. Visual field disturbance from compression on the optic chiasm is the most frequent chief complaint, in addition to headaches. As the main goal of surgery is safe visual tract decompression (with or without gross total resection), ETPS has been shown to be very effective at achieving this outcome [10, 35, 57, 59, 83, 88, 90].

Visual symptoms are present in around 67% of pituitary nonfunctioning adenomas. Loss of visual acuity and cranial nerve palsies from cavernous sinus invasion can amplify the visual disturbance associated with the classic visual field defect – a bitemporal hemianopia. In our review of recent literature [10, 35, 57, 59, 83, 88, 90], ETPS surgery allowed for improvement in visual outcome in almost 80% of the patients, while gross total resection (GTR) was attainable in around 70% of cases (Table 15.1). The volume of the tumor and the invasion of the cavernous sinus were the main obstacles for achieving GTR [26, 59].

Cavernous sinus extension of pituitary adenomas can be found in around 35% of patients. Overall, endoscopic GTR can still reach 30–35% in these patients. Tumors with Knosp Grade 0–2 (none to minimal cavernous sinus invasion) can be considered surgically curable. When ETPS was compared to microscopic resection for Knosp Grade 0–2 tumors, Jane et al. found no statistically significant difference in the extent of resection and endocrinological complications between the two cohorts [10]. The ETPS group did, however, have shorter hospitalizations, but also higher rates of CSF leaks. Failure to achieve GTR is usually associated with the lateral extension of tumor into the cavernous sinus (Knosp 3–4), with recent data suggesting a superiority of the endoscopic approach [35] for these tumors.

Evaluation of residual/recurrence rates can be complex; it depends primarily on the definition of extent of resection and the duration of follow-up. Zhan et al. reported in a series of 313 patients, a global recurrence rate of 11% after 32 months (mean) of follow-up, with an increased risk in younger patients (40–55 years) when compared with the older (>65 years) group (15% vs. 7%) [90]. Table 15.1 summarizes the GTR, visual outcome, and associated complications following ETPS for nonfunctioning adenomas in recently published papers.

Table 15.1 Results and complications of ETPS for nonfunctional pituitary macroadenomas

		# Pts	GTR	STR[a]	CS inv	Visual results				Complications			
Author	Year					Preop VD	Postop VI	Unchanged	Worsened	CSF leak	Perm DI	Endo compl	Meningitis
Karppinen et al. [35]	2015	41	23	–	20	31	30	0	1	1	1	2	0
Zhan et al. [90] - older patients >65	2015	158	120	36	69	158	124	31	3	6	7	15	3
Zhan et al. [90] - younger patients 40-55 yrs	2015	155	119	34	67	155	126	27	2	6	5	13	2
Yildirim et al. [88]	2015	160	144	16	–	69	27	–	–	3	2	2	2
Marenco et al. [50]	2015	25	7	9	20	24	17	7	0	1	0	3	1
Paluzzi et al. [59]	2014	359	239	72	124	189	154	35	0	1	–	16	1
Dallapiazza et al. [10]	2014	56	54	0	–	22	–	–	2	4	0	3	1
Nakao et al. [57]	2011	43	20	23	–	43	42	1	0	4	1	3	–
Total		997	726	190	300	691	520	94	8	26	16	55	10
Percentage			*73%*	*27%*	*35%*	*69%*	*78%*	*20%*	*1%*	*3%*	*3%*	*6%*	*1%*

Pts number of patients, *GTR* gross total resection, *STR* subtotal resection, *CS inv* cavernous sinus involvement, *Preop VD* preoperative visual disturbance, *Postop VI* postoperative visual improvement, *Perm DI* permanent diabetes insipidus, *Endo Compl* postoperative endocrinologic complications

[a]STR: Definition of subtotal resection is variable between studies

Preoperative pituitary dysfunction can be found in approximately 60% of patients. Reports of improvement of preoperative hypopituitarism after surgery are highly variable, ranging from 9 to 55% [15, 35, 50]. Given their large size, apoplexy in macro and giant nonfunctioning pituitary adenomas can represent a life-threatening complication. When diagnosed swiftly, ETPS has been shown to be effective in restoring cranial nerve palsies and visual deficits, while achieving GTR [91].

The main complications associated with ETPS for nonfunctional adenomas are as follows: Postop CSF leak rate of 3%, permanent DI rate of 3%, and meningitis 1% and other postop endocrinologic complication rate of 6%.

Functional Adenomas

Given the nature of their secretions, treatment results for functional adenomas focus more on endocrinologic cure (EC) than gross total resection. Consensus is progressively being established over the remission criteria for the different subtypes [19, 39, 53, 77, 79]. The overall EC achieved by endoscopic endonasal surgery in recent literature is around 60–80% [20, 27, 51, 53, 59, 83]. Microadenomas are more inclined to biological remission, with EC usually superior to 80%, while macroadenoma are frequently harder to treat with EC percentages frequently lower than 60% [20, 24, 51, 53, 59]. Understandably, extension into the cavernous sinus reduces remission rates to less than 40% in most cases [24, 53, 59, 66] (Fig. 15.1a).

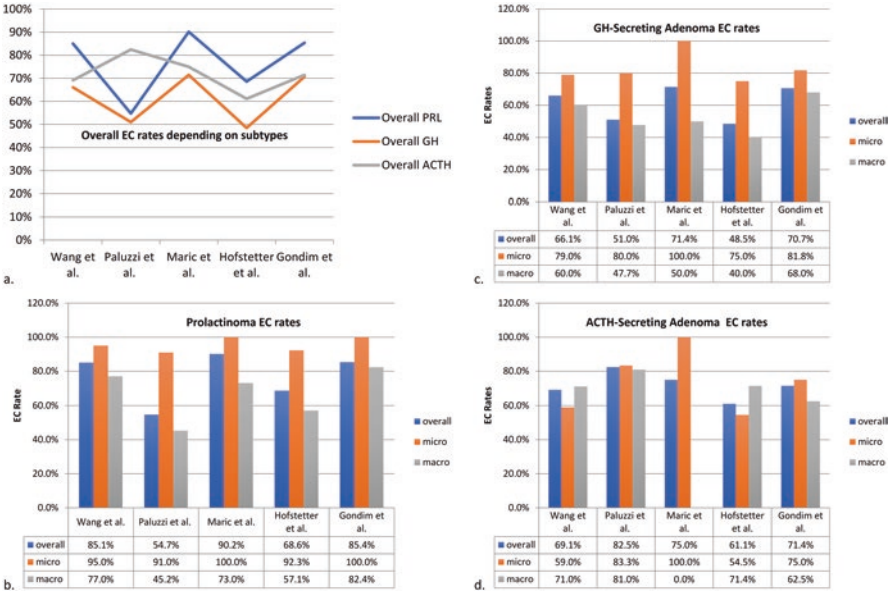

Fig. 15.1 Results of ETPS functional pituitary adenomas (review of the recent literature [20, 27, 51, 59, 83]) (*EC* endocrinologic cure, *PRL* prolactin, *Micro* microadenomas, *Macro* macroadenomas)

Prolactinomas

The majority of prolactinomas are sensitive to dopamine antagonists, however, a nonnegligible amount of tumors still exhibit resistance to medical therapy, necessitating the resort to surgery. A consensus is not yet available, but usually resistance is defined by the failure to attain normoprolactinemia and/or to reach tumor shrinkage of more than 50% after 3 months of maximal medical treatment [55, 85]. Drug response usually correlates to the tumor size. Resistance to bromocriptine and cabergoline is respectively around 10% and 25% for microprolactinomas, and 25% and 30% for macroprolactinomas [55, 81, 82, 85]. Only 21% of patients with microprolactinomas, and 16% of patients with macroprolactinomas demonstrated cure (normal blood prolactin) after treatment withdrawal, underlining the burden of long-term medical treatment [64]. Drug intolerance might also direct patients toward surgical management. A randomized multicenter study of 459 patients found that side effects associated with cabergoline and bromocriptine provoked 3% and 12% of patients respectively to stop their medical treatment [84], leading to surgical management. In cases of apoplexy and acute visual deterioration, surgery should be attempted prior to any medical therapy.

The surgical EC rate of microprolactinomas is predictably high (>90%) (Fig. 15.1a, b). Based on the excellent curative results achieved with surgery, some reports advocate surgical treatment as a first-line treatment in microprolactinomas [8, 32, 73]. A good needed majority of prolactinomas are however discovered at the macroadenoma stage (~60%), and the subsequent EC rate of ETPS is lower at approximately 76% [20, 26, 51, 59, 83] (Fig. 15.1a, b). The cure rate is inversely correlated to tumor size and preoperative prolactin levels [1].

A recent systematic review of the literature failed to identify any strong evidence that preoperative dopamine agonists can have beneficial or harmful effects on surgical results [5]. In residual and recurrent tumors, medical treatment might regain efficacy [25, 59]. In medication-refractory tumors, stereotactic radiosurgery can be proposed. Although stereotactic radiosurgery can control tumor growth, it is still associated with multiple side effects including panhypopituitarism and CN palsies [54].

GH-secreting Adenomas: Acromegaly

Guidelines for the definition of an EC have been updated recently, complicating any analysis of previous papers. Currently, EC is defined by the normalization of IGF-1, with GH levels <0.4 ng/mL after OGTT (oral glucose tolerance test) or GH levels <1 ng/mL when randomly tested [19]. Previously, under the Cortina criteria, a cure was defined as normalization of IGF-1 and GH levels <1.0 ng/mL after OGTT [18]. Unsurprisingly, these more stringent criteria negatively impact the attained EC rates of recent reports. Paluzzi et al. described a drop of EC rates from 65 to 51% when applying the new definition [59]. Interestingly, the drop of EC rates was even larger for cavernous sinus invading macroadenomas (47–15%) [59], underlining the prior underestimation of the invasiveness of these tumors.

GH-secreting adenomas are classically diagnosed at the stage of macroadenoma (~80%), with preoperative and perioperative examination reporting dural invasion of the cavernous sinus in over 50% of patients [25, 59]. This explains the lower rate of EC attained by surgical treatment alone in GH-secreting adenomas (~60%) when compared to other subtypes [20, 26, 51, 59, 83] (Fig. 15.1a, c). In addition to tumor size and invasion of the cavernous sinus as factors influencing postoperative remission [25], high preoperative GH levels have also been shown to be inversely correlated to postoperative remission rates [2]. While intraoperative GH levels are not clinically useful [80], early postoperative normalization of GH levels has been shown to be a good prognosticator of long-term outcome in acromegaly [34, 36].

Somatostatin analogue injections like octreotide and lanreotide, typically administered to patients on a monthly basis, suppress GH production in about 70% and cause tumor shrinkage in 30–50%. These are usually reserved for when first-line surgical treatment is impossible. Even though multiple reports emphasize a positive effect of preoperative medical treatment on short-term postoperative remission, an improvement of long-term ER is still under debate [16, 49, 67, 75]. Surgery still represents the first-choice treatment, since it offers a cost-effective and a safe cure to a good proportion of patients.

When it is not curative, surgery can still allow for tumor debulking, which not only increases the postoperative response to medical treatment [7, 25, 56], but also improves the efficacy of stereotactic radiosurgery treatments, and reduces its side effects. In association with surgery, Paluzzi et al. reported that these adjuvant treatments increased the EC rate in cavernous sinus invading macroadenomas from 15 to 52% [59]. The recurrence rate after long-term EC in acromegaly tends to be lower than other adenomas, but still ranges between 3 and 10% at 5 years follow-up [56, 58]. Reoperation for recurrence can still achieve satisfying results, with 57% of patients reporting EC in a series by Yamada et al. [87].

ACTH-secreting Adenomas: Cushing's Disease

No consensus is available over the biochemical definition of EC in ACTH-secreting adenomas. Differences in preoperative adjuvant medical treatments, postoperative hormonal replacement therapies, and perioperative hormone testing protocols, add to the complexity of any standardization. Current guidelines tend to suggest early hormonal testing while withholding treatment with glucocorticoids, or at least using low nonsuppressive doses [3, 47, 72]. Close monitoring is mandatory to diagnose early and treat any signs of hypoadrenalism [3]. Multiple reports suggest that morning serum cortisol level of <2 μg/dL, UFC (Urine Free Cortisol) of <20 μg/24 h, and ACTH serum level of <5 ρg/mL are highly predictive of long-term remission and low recurrence [3, 23]. Patients with a cortisol level between 2 and 5 μg/dL can still be considered in remission but should have closer hormonal monitoring [3]. Patients with higher cortisol levels are diagnosed with persistent disease.

The EC percentages achieved by surgery alone are usually around 70% [20, 26, 51, 59, 83]. In contrast to prolactin- and GH-secreting adenomas, where the EC rate

is inversely linked to tumor volume, the EC rate in ACTH-secreting adenomas is associated with the identification and resection of small tumors [20, 26, 51, 59, 83] (Fig. 15.1a, d). Even though usually discovered and treated as microadenomas (70%), ACTH-secreting adenomas still display a nonnegligible rate of dural invasion, as reported by Lonser et al. who identified 34% with histologically confirmed dural invasion, while preoperative MRI predicted it in only 4% of these cases [47]. Interestingly, the larger size of the ACTH-secreting adenomas as well as their location in the far lateral potion of the anterior lobe of the pituitary gland was associated with higher rates of dural invasion [47].

If the first surgery is ineffective in achieving EC, either because no tumor was seen on preoperative imaging or because no tumor could be identified intraoperatively, repeated surgery after inferior petrosal sinus sampling is an option. Hemihypophysectomy can be performed if the inferior petrosal sinus sampling localizes the tumor to one side [20]. Surgery is the mainstay of treatment for ACTH-secreting adenomas. Even for recurrent disease, a second surgery offers a reasonable possibility (61%) of immediate remission [63]. If the operation is not successful, other treatments, including pituitary radiation, medical therapy, and even bilateral adrenalectomy, may be required.

Multiple medical therapies are available as a complement to surgical treatment. Various pituitary-targeting drugs (pasireotide, cabergoline), steroidogenesis inhibitors (ketoconazole, metyrapone) and glucocorticoid receptor-blockers (mefeprostone) can be used as first-line medical therapy only when surgery is not an option, or if surgery has failed [9]. The substitutive treatment of postoperative panhypopituitarism can be less disturbing to the quality of life of these patients than some of these drugs.

As in other adenoma subtypes, radiosurgery can represent a useful option when the tumor is locally invasive [59, 83]. Sheehan et al. reported, in a retrospective study of 96 patients, a 70% remission rate after Gamma Knife surgery, with a median time to remission of 16 months [74].

Complications

Complications of endoscopic transsphenoidal pituitary surgery (ETPS) can grossly be divided into the categories of sinonasal, neurologic, infectious, vascular, and endocrine.

In order to access the skull base through the endonasal approach, a significant amount of dissection must occur involving the nasal cavities and sinuses which may lead to postoperative sinonasal complications. Specifically adhesions, septal perforations, epistaxis, and acute and chronic rhinosinusitis may develop [45, 76]. Typically close follow-up by a rhinologist during the first postoperative year can help identify these adverse events and treat them appropriately, either with nasal drops, antibiotics, or more frequent surveillance. Sinonasal quality of life (QOL) following endoscopic pituitary surgery reaches a nadir at two to three weeks and recovers by three months postoperatively [44, 60]. Nasoseptal flap elevation does

not significantly affect QOL [30]. Subtotal resection of tumor negatively impacts postoperative QOL, in both secreting and nonsecreting pituitary adenomas [52].

Once the skull base has been encountered, this site becomes the location of the most common complication of transsphenoidal surgery—a CSF leak. Initial reports of endonasal transsphenoidal surgeries had very high rates of CSF leaks, mostly a result of inadequate repair of the skull base upon completion of the surgery. Advances in vascularized flaps and various multilayer closure techniques have reduced the rate of CSF leak to less than 5% [22, 28, 33, 41, 48], with some centers developing case-specific protocols to drive down the postoperative CSF leak rate close to 0% [62]. Risk factors that predispose a patient to develop postoperative CSF leaks include large skull-base exposures, prior radiation, reoperations, and other intracranial factors which result in elevated intracranial pressures [29].

Usually clinically diagnosed, CSF leaks are characterized by high-volume clear fluid dripping from the nose, which may or may not be position dependent. Less obvious leaks may present more insidiously, with dripping in the back of the pharynx, salty taste or positional headaches which resolve with lying flat. The use of intrathecal fluorescein, usually administered via lumbar puncture or lumbar drain preoperatively, can help identify CSF leaks intraoperatively and in the immediate postoperative period, with a characteristic staining of CSF to a fluorescent yellow-green color [68, 70].

CSF leak also means that there is communication of the nasal cavity and the intracranial compartment, which can lead to pneumocephalus and meningitis. Pneumocephalus can result in mass effect similar to blood or other intracranial lesions. Tension pneumocephalus can be a fatal complication caused by entraining air through the skull-base defect without a release mechanism and should be considered a surgical emergency.[69, 89]. Placement of a lumbar drain should be avoided in this circumstance since it may promote downward herniation. Reoperation for repair of the leak is generally required.

Infection is another concern following endoscopic transsphenoidal surgeries. The rate of infection and CSF inoculation however, is relatively low, despite the fact that the nasal cavity, which is colonized by multiple organisms, is the primary passageway to the sterile intracranial environment. Postoperative meningitis is rare with a reported incidence ranging from 1.6 to 8% [6, 31]. Patients will typically present with meningeal signs including headaches, neck stiffness, and photophobia. Fevers and chills are frequently reported, and laboratory studies may demonstrate elevated WBC, ESR, and CRP. The most common risk factor for meningitis is a postoperative CSF leak. Meningitis without the existence of a leak is extremely rare.

The rate of intracranial abscess formation after endonasal skull-base surgery is quite low [43], as most patients often seek medical attention before the frank development of cerebritis or a walled off abscess. Lastly, as mentioned previously, rhinosinusitis can have less emergent consequences but is reported to occur in about 8% of patients undergoing endoscopic transsphenoidal procedures [6].

Vascular injury and cerebrovascular accidents are also rare but potentially catastrophic complications of transsphenoidal pituitary surgery. Minor bleeding is frequently encountered during these procedures, usually from the nasal mucosa,

sinonasal arteries, and bone bleeding, which can typically be controlled with cautery or bone wax. Once through the floor of the skull base, venous bleeding from the cavernous sinus may be encountered which can be tamponaded through packing or other hemostatic agents.

Injury to the internal carotid artery, though rare (<0.125%), is the gravest complication in any transsphenoidal surgery and can lead to exsanguination and stroke if not dealt with expeditiously [17, 37, 61, 71]. Long-term sequelae of internal carotid injury may also occur, including pseudoaneurysm carotid-cavernous fistula formation [17, 21]. Although several techniques have been proposed to control an arterial injury, the most reliable is packing and endovascular occlusion of the artery [71].

Lesions with suprasellar extension such as large pituitary adenomas, craniopharyngiomas, and meningiomas may be intimately involved with the circle of Willis and various perforating vessels. In these situations, large-territory strokes are exceedingly rare, but possible. Therefore, identification and careful preservation of the anterior and posterior cerebral arteries, recurrent arteries of Heubner, and anterior and posterior communicating arteries is of utmost importance. Arterial injury can often lead to subarachnoid hemorrhage, which can in turn lead to seizures and development of hydrocephalus.

Neurologic complications encountered postoperatively are primarily attributed to cranial neuropathies. While many patients with pituitary tumors may present with varying degrees of visual field deficits and ophthalmoplegia, the incidence of these developing postoperatively is still relatively low, on the order of 1–2% [6, 65]. Even when surgery is performed in the cavernous sinus, the rate of permanent cranial neuropathy is nearly 0% with a rate of transient neuropathy of 5.6% [86]. The abducens nerve is the most medially oriented cranial nerve within the cavernous sinus and, therefore, can be injured leading to a lateral gaze palsy. Inadvertent breaches through the lamina papyracea can injure the medial rectus muscle leading to weakness of ipsilateral medial gaze and diplopia [4].

The optic nerves and chiasm may be intimately involved with larger pituitary tumors and require careful dissection to prevent any injury. In addition to careful preservation of the nerves themselves, the tenuous blood supply to these nerves must be respected as inadvertent thermal injury can lead to ischemic complications and permanent visual defects. The same holds for the ophthalmic artery, which branches from the ICA after it emerges from the cavernous sinus. Injury to this vessel can also lead to unilateral blindness, though robust collateral circulation can circumvent this complication in some cases [42, 78].

Orbital/retro-orbital hematomas occur in less than 1% of endoscopic transsphenoidal surgeries and can present with any combination of unilateral or bilateral ophthalmoplegias. This complication is time sensitive and the rate of neurologic recovery is proportional to the time of decompression. Any unexplained postoperative ophthalmoplegia, visual acuity decline, or progressive proptosis should be immediately investigated with imaging.

Endocrinopathies may present postoperatively as a result of manipulation of the pituitary gland and stalk or disruption of blood supply to the organ. Preoperative endocrine labs should be assessed on all patients to establish a baseline. The frequencies of

postoperative anterior pituitary insufficiency is highly variable between reports. The average is approximately 6% (Table 15.1), but rates seem to get lower in specialized high-volume centers at around 2–3% [13, 25, 59]. Postoperative anterior hypopituitarism is also correlated to the tumor size, particularly when the adenoma is larger than 20 mm [12, 14]. Giant adenomas are even at a higher risk with around 5–9% of postoperative deficiencies [33, 38, 57]. Frequently more than one axis is impaired. The corticotropic axis seems to be the most frequently damaged, followed by the thyrotrophic [59]; this observed propensity is probably skewed due to the important functional role of these axes in adults.

Diabetes insipidus (DI) is the most frequently encountered endocrinopathy in transsphenoidal pituitary surgery. About 4–20% of individuals may experience transient DI whereas 1–5% experience permanent DI [77]. This occurs from disruption of the posterior pituitary gland, pituitary stalk, or other fibers arising from the hypothalamus which leads to dysregulation of antidiuretic hormone (ADH). This results in disruption of water balance regulation leading to dehydration and hypernatremia. Postoperative net fluid balance, urine specific gravity, hourly urine output, and frequent sodium levels should be carefully monitored, and appropriate treatment with desmopressin instituted. Giant adenoma appears to be associated with an increased risk for developing postoperative permanent DI with incidence rates stretching to 10% [12, 38, 57].

The second most frequent endocrinopathy following transsphenoidal surgery is hypocortisolemia. Decreased release of ACTH from the pituitary axis results in low levels of circulating cortisol, which is best assessed in the morning hours of postoperative days 1 and 2. Hypocortisolemia can result in mild gastrointestinal symptoms, dizziness, fatigue, and headaches, but can progress to severe hypotension without treatment. For those patients who become hypocortisolemic postoperatively, steroid replacement therapy should be initiated, typically with hydrocortisone twice daily.

Conclusion

As advances in lens technology and extended instrumentation have evolved over the past two decades, endoscopic transsphenoidal surgery, for pathologies of the sellar and suprasellar region, has become a valuable commodity to the skull-base surgeon. This approach allows for excellent visualization and safe resection with relatively few complications compared to traditional open microneurosurgical approaches.

Endoscopic transsphenoidal pituitary surgery (ETPS) has excellent outcomes, with gross total resection (GTR) rates upward of 70% for nonfunctioning macroadenomas, and endocrinologic cure rates of 60–80% for functional tumors. The GTR rates are higher for smaller tumors and those without cavernous sinus invasion. For tumors invading the cavernous sinus, the outcomes for ETPS are superior to that of microscopic transsphenoidal pituitary surgery. With further refinement in endoscopic technology (3D endoscopes) and endoscopic instrumentation, along with increased operator proficiency, outcomes for ETPS will continue to improve with time.

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Intraoperative Imaging for Pituitary Surgery

16

Peter T. Sylvester and Michael R. Chicoine

Introduction

Pituitary adenomas are benign tumors that account for 10–15% of intracranial neoplasms [1, 2]. These tumors often are benign incidental findings, but can cause significant morbidity through excess hormone production or mass effect on the optic chiasm or other adjacent structures. Surgery via the transsphenoidal route remains the primary treatment, with craniotomy approaches reserved for more extensive tumors. Maximal safe resection is typically the goal of any surgical procedure for pituitary adenomas. Both endoscopic and microscopic approaches have been described [3, 4], but regardless of the technique utilized, there is potential for the surgeon to unintentionally leave residual tumor. Large case series from experienced centers report subtotal resection in 20% or more of cases [5]. Incomplete tumor resection can be due to several factors including large tumor size, invasion into normal brain structures (e.g., cavernous sinus, suprasellar space), and tumor consistency. Incomplete resection may lead to additional surgeries, radiation treatments, or other medical therapies for the patient. A number of strategies are utilized in an effort to maximize safe adenoma resection including optimizing surgical exposure, using stereotactic navigation to confirm anatomical landmarks and predict the extent of removal [6], and implementing endoscopy to provide a high-resolution panoramic view of the surgical field, but despite these approaches, incomplete tumor removal is still a potential issue.

Intraoperative imaging is used frequently in many surgical specialties including neurosurgery to verify that the surgical goals are optimally achieved such as intraoperative fluoroscopy to confirm appropriate positioning of spinal instrumentation or

P.T. Sylvester, MD • M.R. Chicoine, MD (✉)
Department of Neurological Surgery, Washington University School of Medicine, St. Louis, MO, USA
e-mail: chicoinem@wudosis.wustl.edu

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_16

intraoperative catheter angiography to verify obliteration of a cerebral aneurysm [7, 8]. Quality assurance with imaging is a well-established strategy to improve the safety and efficacy of many surgical procedures. A variety of intraoperative imaging modalities have been pursued to enhance safe resection for different types of brain tumors, particularly gliomas and pituitary adenomas, by identifying residual tumor that can be resected prior to completion of the surgical procedure. Such methods have been demonstrated to improve the extent of resection (EOR) and improve patient outcomes [9–11]. This chapter will review established and developing intraoperative imaging techniques that are used to verify maximal resection of pituitary adenomas including low-field and high-field intraoperative magnetic imaging (iMRI), intraoperative computed tomography (iCT), intraoperative ultrasound (iUS), and fluorescence enhancement of endoscopic and microsurgical visualization.

Intraoperative MRI

The use of intraoperative imaging for pituitary adenoma resection has been studied by a number of centers, including studies reporting improved extent of resection (EOR) using either low-field or high-field iMRI. An article by Buchfelder et al. [12] in 2012 summarized prior studies evaluating low- and high-field iMRI use during pituitary adenoma resection. Also evaluated in this article was the impact of iMRI in combination with stereotactic neuronavigation and endoscopy during transsphenoidal surgery. These authors concluded that there are a number of available iMRI strategies each with inherent benefits and limitations with regard to improving safe maximal resection of pituitary adenomas.

Basic Setup

A variety of iMRI devices have been used at different centers to assess the EOR of pituitary adenomas. One of these strategies was the original “double donut” iMRI used by Dr. Black and colleagues, where the patient and surgeons were positioned within the bore of a low-field magnet [13, 14]. Other strategies included devices that either moved the patient to the magnet or moved the magnet to the patient. Examples of these strategies will be explained in a later section.

The introduction of an iMRI magnet into the operating theater also created challenges with surgical instrument management. Operating suites for iMRI have been designed such that all of the surgical instruments are made of nonferromagnetic MRI-compatible materials such as titanium, or alternatively such that all standard surgical instruments can be used, but then removed from the field at the time of the iMRI acquisition. Because of the risk of ferromagnetic objects becoming projectiles in strong magnetic fields, risks of electromagnetic fields generating excessive heat, and other potential safety risks, the iMRI working environment requires a number of procedural modifications before, during, and after surgery such as checklists and personnel training, physical adaptations of the various types of instruments and equipment used in and around the operating room, and anesthetic considerations [15–20].

Other standard operating room equipment also required modification to accommodate iMRI devices, such as special anesthesia and cardiopulmonary monitoring equipment. Durable operating room equipment such as head immobilization devices and operating room tables required numerous modifications to ensure no interference with the magnetic flux lines and allow safe movement of the anesthetized, sterile patient into the bore of the magnet. All of these modifications improve the ability to safely obtain intraoperative MRI studies, but can potentially limit the utility of these operating rooms for other standard surgical procedures.

Low-Field iMRI (Less Than 1.5 Tesla)

Low-field iMRI typically refers to configurations using a magnet field strength less than 1.5 Tesla (1.5 T; Table 16.1). The first such device was the "double donut" concept [13]. This was developed by General Electric and used initially in Boston and then in a few other centers as well [21–24]. With this strategy, the patient was in the bore of the two parallel donut-like structures (Fig. 16.1a). In the narrow space between these two ring structures on either side of the patient, the surgeon could stand and perform surgery within the magnet itself. This strategy of "operating in the magnet" required that all of the surgical instruments and other equipment be

Table 16.1 Studies evaluating <0.5 Tesla intraoperative MRI for pituitary adenoma surgery

Authors	Tesla	Scanner type	Cases
Vitaz et al. (2011)	0.50	GE Signa SP	100
Ramm-Pettersen et al. (2011)	0.50	GE Signa SP	20
Martin et al. (1999)	0.50	GE Signa SP	5
Theodosopoulos et al. (2010)	0.30	Hitachi AIRIS II open	27
Bohinski et al. (2001)	0.30	Hitachi AIRIS II open	29
Fahlbusch et al. (2001)	0.20	Siemens Magnetom open	44
Steinmeier et al. (1998)	0.20	Siemens Magnetom open	16
Kim et al. (2013)	0.15	Polestar N20	229
Hlavica et al. (2013)	0.15	Polestar N20	101
Berkmann et al. (2012)	0.15	Polestar N20	60
Czyz et al. (2011)	0.15	Polestar N20	17
Berkmann et al. (2011)	0.15	Polestar N20	32
Baumann et al. (2010)	0.15	Polestar N20	6
Bellut et al. (2010)	0.15	Polestar N20	37
Tabakow et al. (2012)	0.15	Polestar N20	18
Wu et al. (2009)	0.15	Polestar N20	55
Ahn et al. (2008)	0.15	Polestar N20	63
Gerlach et al. (2008)	0.15	Polestar N20	40
Schwartz et al. (2006)	0.12	Polestar N10	15
Anand et al. (2006)	0.12	Polestar N10	10
Hadani et al. (2001)	0.12	Early Polestar	20

Fig. 16.1 "Double doughnut" low-field intraoperative MRI strategy first employed in Boston. (Figure from General Electric Inc. promotional materials) (**a**). Open low-field intraoperative MRI strategy situated so that patients can be transported into position from the adjacent operating room to acquire MRI images (Figure from Hitachi, Inc. promotional materials) (**b**). Polestar^{tm} low-field intraoperative MRI strategy model N20 (**c**) and N30 (**d**). The Polestar^{tm} strategy is a device that can be situated beneath the operating table and elevated into the imaging position as needed to acquire images (Figures **c, d** of the Polestar^{tm} systems from Medtronic, Inc. promotional materials)

made of MRI-compatible nonferromagnetic materials. There were some limitations and constraints in this setup in that working space was narrow and the operative positioning options were fewer than in a standard operating room. One major potential advantage of this configuration that has not been matched by any other such modality since was the ability to frequently and repeatedly obtain MRI images throughout the surgical procedure in a matter of minutes. Nonetheless, because of many logistic limitations, the "double donut" modality has not been accepted as a practical solution, but did lay much of the groundwork upon which future iMRI solutions have been based.

The "open MRI" configuration including examples such as the 0.3 T Hitachi AIRIS II^{tm} [25, 26] (Fig. 16.1b) and the 0.2 T Siemens Magnetom^{tm} [27, 28] are other low-field iMRI options. With this format, the surgery was performed in an adjacent room and then the patient was moved into the MRI suite for image acquisition as needed during surgery.

The Polestar^{tm} platform offered another low-field iMRI option. This system was originally developed by Odin in Israel [29], then purchased by Medtronic, who later developed several versions including the 0.12 T N10 [30, 31], the 0.15 T N20 [32–41], and the 0.26 T N30 devices (Fig. 16.1c, d). Several additional modifications and upgrades were made including integration of a surgical navigation system.

Of the low-field iMRI options, this platform has been the most reported on and likely represents the best compromise between form and function. This device is a much smaller apparatus than other devices and can fit beneath the operating room table or be stored in a smaller storage space adjacent to the operating room. This device is considerably less costly and required fewer major modifications of the operating room. It has been considered by some to be cumbersome when stored beneath the operating room table.

The advantage of some of the low-field systemsiMRI has been that they can be potentially be less costly and may require fewer modifications of the surgical environment. Some of the disadvantages of the lower iMRI techniques include images with a smaller field of view and lesser degrees of image resolution, which, in particular for the intricate small anatomical area of the pituitary, potentially could be a challenge.

High-Field iMRI (1.5 Tesla and Greater)

The high-field iMRI systems generally include either a 1.5 T [10, 42–51] or 3.0 T magnet (Table 16.2) [52–59]. These high-field systems have included devices such as that developed by Brainlab[tm], in which the magnet is in the operating room and

Table 16.2 Studies evaluating 1.5 Tesla or greater intraoperative MRI for pituitary adenoma surgery

Author	Tesla	Scanner type	Cases
Fomekong et al. (2014)	3.0	Phillips Integra	73
Qiu et al. (2012)	3.0	Siemens Magnetom Verio	55
Lang et al. (2011)	3.0	Siemens Magnetom Verio	9
Netuka et al. (2011)	3.0	General Electric Signa HDx	86
Pamir et al. (2011)	3.0	Siemens Magnetom Trio	42
Jankovski et al. (2008)	3.0	Philips Achieve	3
Hall et al. (2006)	3.0	Philips Gyroscan ACS-NT	77
Pamir et al. (2006)	3.0	Siemens Magnetom Trio	10
Sylvester et al. (2015)	1.5	Siemens Magnetom Espree	156
Li et al. (2015)	1.5	Siemens Magnetom Espree	30
Berkmann et al. (2014)	1.5	Siemens Magnetom Sonata Maestro	111
Berkmann et al. (2014)	1.5	Siemens Magnetom Sonata Maestro	85
Coburger et al. (2014)	1.5	Siemens Magnetom Espree	76
Paterno et al. (2014)	1.5	Siemens Magnetom Espree	72
Tanei et al. (2013)	1.5	Siemens Magnetom Symphony	14
Szerlip et al. (2011)	1.5	Siemens Magnetom Espree	53
Meng et al. (2011)	1.5	Siemens Magnetom Espree	30
Nimsky et al. (2006)	1.5	Siemens Magnetom Sonata Maestro	129
Fahlbusch et al. (2005)	1.5	Siemens Magnetom Sonata Maestro	23
Dort et al. (2001)	1.5	Magnex Scientific	15

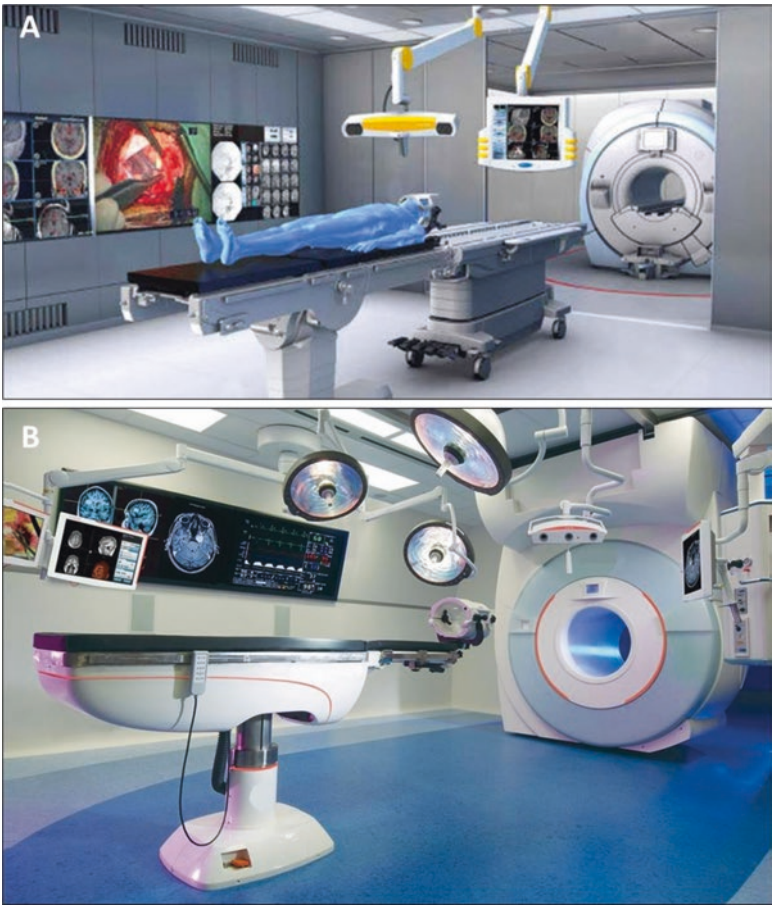

Fig. 16.2 High-field intraoperative MRI configuration including the Brainlab[tm], which involves movement of the patient to a fixed-position magnet (**a**), and the IMRIS[tm] (**b**) (Figures from Brainlab, Inc., and IMRIS, Inc. promotional materials respectively)

the patient is moved to the imaging device on a special table (Fig. 16.2a). With this strategy, surgery can be performed with standard instruments removed a short distance in the operating room from the magnet.

Another high-field iMRI option is the movable magnet concept developed by Sutherland and colleagues in Calgary [60, 61]. The movable iMRI strategy involves a ceiling-mounted iMRI device in a room adjacent to one or more operating rooms. This device can be moved into the operating room as needed for imaging, but surgery can be performed with standard instruments when the magnet is out of the room. This movable iMRI solution led to the formation of the company IMRIS[tm], Inc., which has developed a number of 1.5 and 3.0 T variations of this concept (Fig. 16.2b).

Advantages of the high-field iMRI systems are that they can provide high-resolution imaging of a quality equivalent to the diagnostic imaging that is typically used for pituitary adenomas and other types of brain tumors. There is typically greater inherent cost associated with the implementation of high-field iMRI compared to the low-field devices. Furthermore, more extensive modifications to the operating room environment may be needed in order to implement these high-field iMRI devices. Patients with pacemakers, other non-MRI-compatible implants, and morbid obesity may not be candidates for iMRI.

In general, the high-field MRI devices offer more clinical versatility than low-field scanners. High-field systems have the potential to perform advanced imaging modalities such as diffusion tensor imaging or cine dynamic flow sequences; however, these sequences do not necessarily apply to most pituitary adenoma surgeries. Some of high-field systems are configured for the dual purpose of intraoperative and standard diagnostic imaging, which can help defer some of the additional cost of these devices. In addition, other surgical procedures are being integrated into the high-field MRI, including functional neurosurgery procedures for movement disorders [62–64] and interstitial laser ablations from brain tumors, epilepsy, and other lesions [65–69].

Washington University Experience

In 2008, Washington University and Barnes-Jewish Hospital in St. Louis installed a movable high-field 1.5 Tesla iMRI device (IMRIS^{tm}, Inc., Winnipeg, Manitoba, CA). This device is situated between two operating rooms and can be transported to the patient by a ceiling-mounted rail system as needed for intraoperative imaging (Fig. 16.3a–d). Preoperatively, it is our practice to merge baseline CT and MRI images acquired in the days before surgery into the intraoperative stereotactic navigation system (Fig. 16.4). An iMRI scan is performed after maximum safe resection, and these images are then merged with the preoperative CT and MRI to assess EOR and to facilitate further dissection and tumor resection if indicated.

Since installation, the iMRI scanner at Barnes-Jewish Hospital has been used in over 1400 neurosurgical procedures including over 400 endonasal endoscopic approaches for pituitary adenomas and a variety of benign and malignant skull base tumor resections. Pre-, peri-, and postoperative data for these cases have been collected in an institutional database. In recent years, the Washington University neurosurgery group has been coordinating an IMRIS^{tm}, Inc.-funded multicenter prospective registry called I-MiND (IMRIS^{tm} Multicenter Intraoperative MRI Neurosurgery Database). Data from I-MiND will be used to evaluate the efficacy and cost-effectiveness of iMRI for different patient populations and disease processes.

Multimodality Image Integration

Advanced neurosurgical navigation systems enable the integration of a variety of preoperative in intraoperatively acquired imaging modalities including high-resolution CT and MRI sequences as well as more rapidly accessible lower-resolution

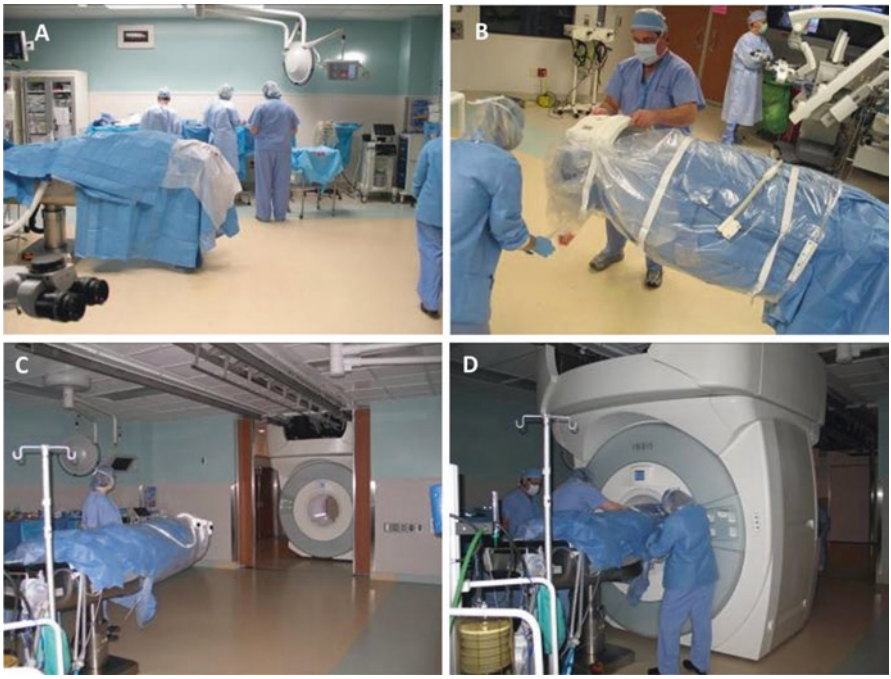

Fig. 16.3 Sequential images of iMRI process for a patient undergoing surgery in the IMRIS[tm] high-field iMRI at Barnes-Jewish Hospital in St. Louis [70]. After the initial resection is completed prior to initiation of the surgical closure, the patient is draped for placement into iMRI scanner (**a**), followed by placement of the head coil which enables image acquisition (**b**). The 6-ton ceiling-mounted movable iMRI device is brought into the surgical suite and positioned over the patient to initiate high-resolution imaging (**c**, **d**)

techniques such as intraoperative ultrasound and fluorescence imaging. The Amigo[tm] suite in Boston is a particularly unique device that enables integration of iMRI, iPET-CT, and biplanar fluoroscopy for intraoperative cerebral angiography (iAngio). Although a rare event, surgical and endovascular management of intraoperative arterial injury during endonasal surgery for pituitary adenoma could be best facilitated by the implementation of a variety of these modalities such as iCT to assess for intraoperative hemorrhage, iAngio to assess and manage (i.e., coiling, stenting, etc.) arterial injury as might occur with an injury of an internal carotid artery, iMRI to assess the adequacy of the tumor resection, as well as the presence of cerebral infarction using diffusion-weighted imaging [71].

Intraoperative MRI and Endoscopy

Prior publications by Theodosopolous et al., Anand et al., and Schwartz et al. have demonstrated complementary efficacy of endoscopy and iMRI, which has been our experience as well [26, 30, 31]. Analysis of pituitary adenoma cases from our

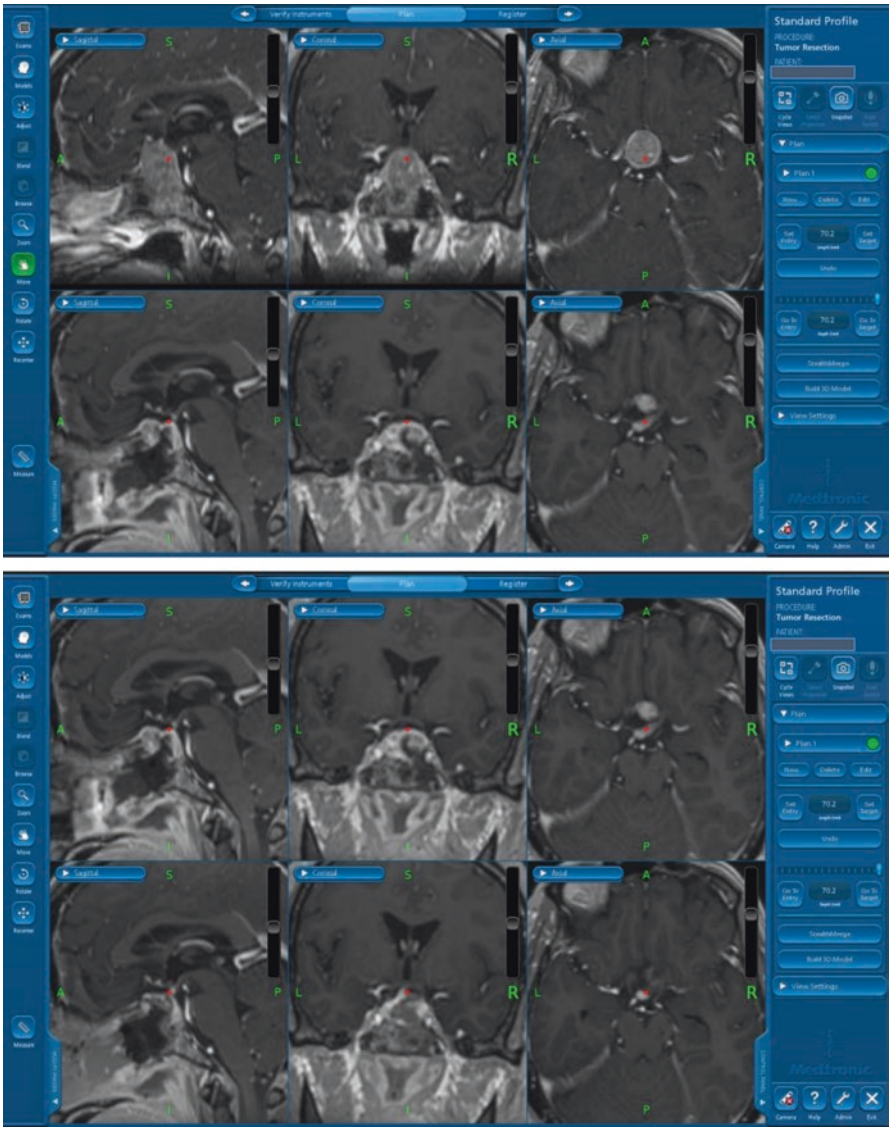

Fig. 16.4 Patient with large nonfunctioning pituitary macroadenoma. The first screen capture from the Medtronic Stealth^{tm} surgical navigation software shows the large macroadenoma on the preoperative MRI integrated into the workstation (*top row*). The *bottom row* shows the first iMRI study integrated into the workstation showing the small superior residual nodule after the initial endonasal endoscopic resection was completed. Additional surgery was performed after the first iMRI, and the endonasal approach was expanded including the removal of additional bone in the region of the tuberculum sella providing access to remove the remaining tumor. The second surgical navigation screen capture shows the first iMRI (*top row*) compared to the second iMRI (*bottom row*) after the small remaining nodule was successfully removed, thereby demonstrating a more complete resection achieved with the use of the iMRI (Images created with assistance from Jeri Bross, Medtronic Inc.)

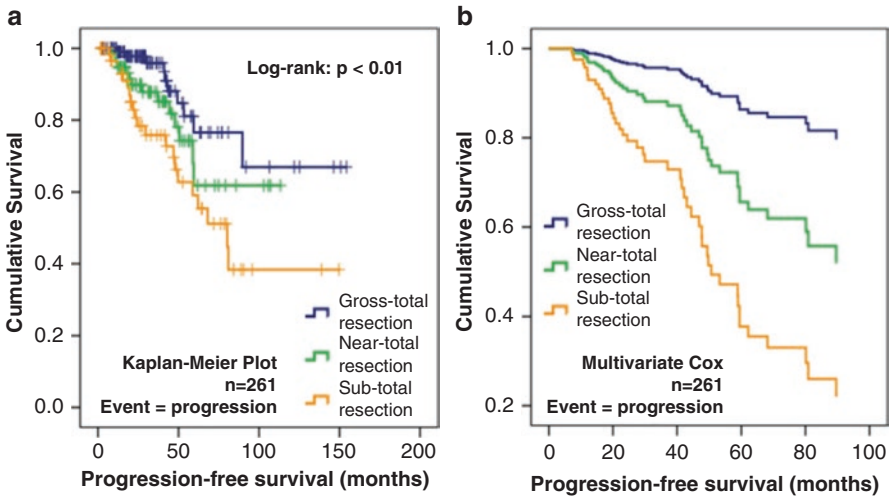

Fig. 16.5 Progression-free survival plots stratified by the extent of resection for univariate (**a**) and multivariate (**b**) analyses (Figure borrowed from *Journal of Neurosurgery*, Sylvester et al. with permission [10])

institution revealed that iMRI prompted further resection in approximately 35–40% of cases, with approximately 10% of patients receiving an increased EOR status (from subtotal to near or gross total, or near total to gross total). Multivariate analysis revealed that the combination of iMRI and endoscopy increased EOR status compared to conventional microsurgery without iMRI. Data from our center also suggests that increased EOR lengthens progression-free survival when controlling for prognostic baseline factors such as recurrent tumor, cavernous sinus invasion, and tumor size (Fig. 16.5) [10].

Cost-Effectiveness of iMRI for Pituitary Surgery

Few studies have evaluated the cost-effectiveness of iMRI for general use, and to date, no studies have reported the specific cost-effectiveness of iMRI for pituitary adenoma resection. Makary et al. [72] evaluated the general use of a low-field iMRI scanner in clinical practice and found no significant clinical benefit from a cost-effectiveness perspective. Improved extent of resection afforded by the use of iMRI and the decreased need for additional surgical and nonsurgical treatments in theory should lead to resultant cost savings, but as of yet, this theoretical cost savings have not been proven.

Limitations of Current Studies

There are limitations to many of the studies evaluating iMRI including the potential for selection and treatment bias due to nonrandomization and use of surrogate markers of patient benefit as primary endpoints. The use of EOR as a surrogate marker

for patient benefit during pituitary adenoma resection may also be particularly problematic for a number of reasons. First, these are slow-growing benign neoplasms that often do not progress or recur after resection. Second, there are several postoperative adjuvant therapies (e.g., radiation, hormone-suppressive medication) that are both safe and effective for controlling residual and recurrent disease in certain situations. Third, several additional surgical tools (i.e., operative endoscope, stereotactic neuronavigation) have been incorporated into the operating room in recent years with EOR benefit that potentially overlaps with iMRI. These confounding factors potentially impact the ability to accurate assess the impact of iMRI upon outcomes for patients undergoing surgeries for pituitary adenomas.

Other Modalities

Intraoperative CT

Some investigators have argued that intraoperative CT (iCT) could be a viable alternative to iMRI for a number of centers [73–76]. A prospective study by Lee et al. [74] compared residual tumor volume determined from iCT (MDCT) to postoperative 1.5-Tesla MRI for 33 patients that received endoscopic resection of pituitary macroadenomas (Fig. 16.6). They found a strong correlation in tumor volumes between modalities for gross-total (R^2 = 0.971) and subtotal resected tumors (R^2 = 0.957), and concluded that iCT could be used effectively for pituitary adenoma resection with similar efficacy to iMRI. These results seem to support that iCT might be a suitable alternative iMRI for pituitary adenoma resection; however, further assessment is warranted.

Intraoperative CT offers potential advantage over iMRI in that it is quick and easy to obtain CT images compared to MRI images. Portable iCT devices exist that can be moved in and out of most standard neurosurgery operating rooms. These scanners can often be used with a variety of standard operating room tables. In

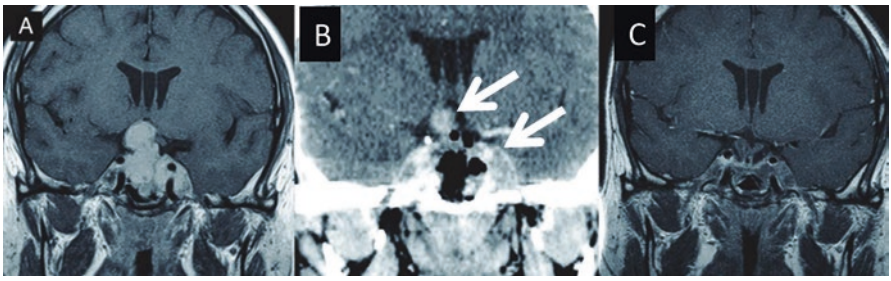

Fig. 16.6 Comparison of preoperative MRI (**a**), intraoperative CT scan (**b**), and postoperative MRI (**c**) in the evaluation of pituitary macroadenoma before, during, and after surgery (Adapted from Lee et al. 2011 with permission (pending) [74]). *Arrows* denote areas of residual adenoma identified with intraoperative CT including the left cavernous sinus and the suprasellar region

addition, iCT mechanistically offers superiority over iMRI in the ability to assess osseous anatomy. CT imaging in general does offer some potential for greater accuracy with stereotactic surgical navigation system reference. Some of the advantages of both CT and MRI can be utilized by digital merging of CT and/or MRI scans preoperatively [76].

Some of the disadvantages inherent to iCT include typically poorer resolution than iMRI particularly for the intricate anatomy of the sellar and parasellar regions. Furthermore, there is some risk of radiation exposure to the patient and operating room personnel with iCT, but with contemporary devices and careful application of imaging, this risk can be limited to acceptably low levels.

Intraoperative Ultrasound

The technique of intraoperative ultrasound (iUS) has shown to be feasible and reasonably sensitive for pituitary adenoma resection and may be a useful adjunct during pituitary adenoma resection. Only a few studies could be identified that used iUS [77, 78], and it seems this technique has not gained widespread use as an adjunct during pituitary adenoma resection. Reportedly, this technique could be used effectively in combination with MRI and inferior petrosal sinus sampling to identify the location of functional microadenomas [77]. In theory, the combination of iUS with other intraoperative imaging modalities could take advantage of the ability to frequently recheck resection status with iUS and then perform a final check with the more sensitive iCT or iMRI. Based on the available studies, the main disadvantages of iUS include poor resolution and dependence on operator experience. Further study is needed, as this technique may be particularly useful during endoscopic or microscopic pituitary adenoma resection cases that suffer from limits in direct tumor visualization.

Nonradiographic Imaging

Use of nonradiographic intraoperative imaging modalities such as fluorescence-guided resection with aminolevulinic acid (5-ALA) or indocyanine green videography (ICGV) has been reported on a limited basis. Preliminary reports have suggested that ICGV might help guide the surgeon to determine the limits of a tumor during pituitary adenoma resection [79, 80]. These reports have assessed this methodology in small series of patients and thus far are not generally applicable until further studied.

Summary

Intraoperative imaging during surgery for pituitary adenomas can be performed using a variety of modalities including iMRI, iCT, iUS, fluorescence imaging technique with 5-ALA, and ICG in an effort to improve the extent of safe tumor

resection. Each of these techniques offers inherent advantages and disadvantages. These techniques are not mutually exclusive and can be used together in a variety of fashions and also further integrated into stereotactic navigation devices, advanced endoscopic visualization, and other surgical techniques. The implementation of these various intraoperative imaging modalities offers real potential to improve upon the extent of safe resection of pituitary adenoma. As these modalities continue to mature, the benefits and ease by which these strategies may be harnessed will certainly only continue to improve.

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The Role of Endoscopic Transsphenoidal Surgery in the Management of Complex Lesions Involving the Skull Base

17

James K. Liu, Eleonora F. Spinazzi, Jean Anderson Eloy, and William T. Couldwell

Introduction

Since the repopularization of the transsphenoidal approach by Guiot and Hardy [1–7], most surgeons have adopted this technique as the primary method for the removal of pituitary adenomas. With the development of modern microinstrumentation, the use of the operating microscope, and advances in endoscopic endonasal instrumentation and navigation, the endonasal transsphenoidal approach has become the preferred method for targeting sellar and parasellar lesions [8–15]. Such predilection in surgical modality is the result of interdependent evolutions in transsphenoidal surgical techniques and imaging technology. While the endoscopic endonasal transsphenoidal approach has

J.K. Liu, MD (✉)
Department of Neurological Surgery, Rutgers New Jersey Medical School, Newark, NJ, USA

Center for Skull Base and Pituitary Surgery, Neurological Institute of New Jersey, Rutgers New Jersey Medical School, Newark, NJ, USA

Department of Otolaryngology-Head & Neck Surgery, Rutgers New Jersey, New Jersey Medical School, Newark, NJ, USA
e-mail: james.liu.md@rutgers.edu

E.F. Spinazzi, BA
Department of Neurological Surgery, Rutgers New Jersey Medical School, Newark, NJ, USA

J.A. Eloy, MD
Department of Neurological Surgery, Rutgers New Jersey Medical School, Newark, NJ, USA

Center for Skull Base and Pituitary Surgery, Neurological Institute of New Jersey, Rutgers New Jersey Medical School, Newark, NJ, USA

Department of Otolaryngology-Head & Neck Surgery, Rutgers New Jersey, New Jersey Medical School, Newark, NJ, USA

Department of Ophthalmology and Visual Science, Rutgers New Jersey Medical School, Newark, NJ, USA

W.T. Couldwell, MD, PhD
Department of Neurosurgery, University of Utah, Salt Lake City, UT, USA

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_17

provided a minimally invasive, direct midline trajectory to sellar and parasellar pathology, recent modifications and extensions to the transsphenoidal approach have expanded its original indication to a larger variety of ventral skull base pathologies [16–19].

Lesions of the skull base, particularly the anterior skull base, the clivus, the cavernous sinus, and the parasphenoid region, can be readily accessed when the exposure of the standard microsurgical transsphenoidal approach is extended with additional bone removal (extended transsphenoidal approach) [10, 12, 20–28]. Depending on the extent and location of the lesion, transsphenoidal approaches can be used alone or in combination with other skull base approaches. The procedure can be performed microsurgically, endoscopically, or both. The standard microsurgical transsphenoidal approach is favorable for midline sellar lesions, such as pituitary tumors and Rathke's cleft cysts, which may extend into the suprasellar region, the clivus, or the sphenoid sinus and nasal cavity. The surgical exposure of the microsurgical transsphenoidal approach can be extended further with additional bone removal and repositioning of the nasal speculum (extended transsphenoidal approach) to access the suprasellar region, clivus, and cavernous sinus. When the endoscope is used as an adjunct to the microscope (endoscopic assistance), exposure can be broadened extrasellarly in the sagittal plane but remains limited laterally by the blades of the nasal speculum. The speculum-based microsurgical extended transsphenoidal approach allows the neurosurgeon to access midline lesions at the planum sphenoidale (anteriorly), the suprasellar cistern and optic apparatus (superiorly), the cavernous sinus and carotid arteries (laterally), and the inferior clivus and foramen magnum (inferiorly).

Exposure beyond the parasellar region in the sagittal and coronal planes can be achieved when the extended transsphenoidal approach is performed using a purely endoscopic endonasal approach (EEA) without a nasal speculum [2]. With the recent advent of extended EEAs, access to a variety of skull base lesions outside of the sella and sphenoid sinus can be accomplished [29–32]. In the sagittal plane, ventral pathology can be accessed from the frontal sinuses anteriorly to the odontoid process posteroinferiorly. In the coronal plane, lateral access can be achieved to remove lesions occupying the cavernous sinus, infratemporal fossa, middle fossa, and petrous apex. Various endoscopic endonasal corridors have been developed to access a desired target of the ventral skull base. The majority of these EEAs share a common initial transsphenoidal approach to the ventral skull base before branching out into their respective paths along the sagittal or coronal plane. They provide a minimal-access technique that avoids a craniotomy and prolonged brain retraction. In this chapter, the authors discuss the various endoscopic endonasal corridors that allow access to a wide variety of complex skull base lesions.

Endoscopic Endonasal Corridors

Sagittal Plane Approaches

EEAs in the sagittal plane include the transcribriform, transplanum transtuberculum, transsellar, transclival, and transodontoid corridors (Fig. 17.1). These approaches can be used alone or in combination, according to the extent of the

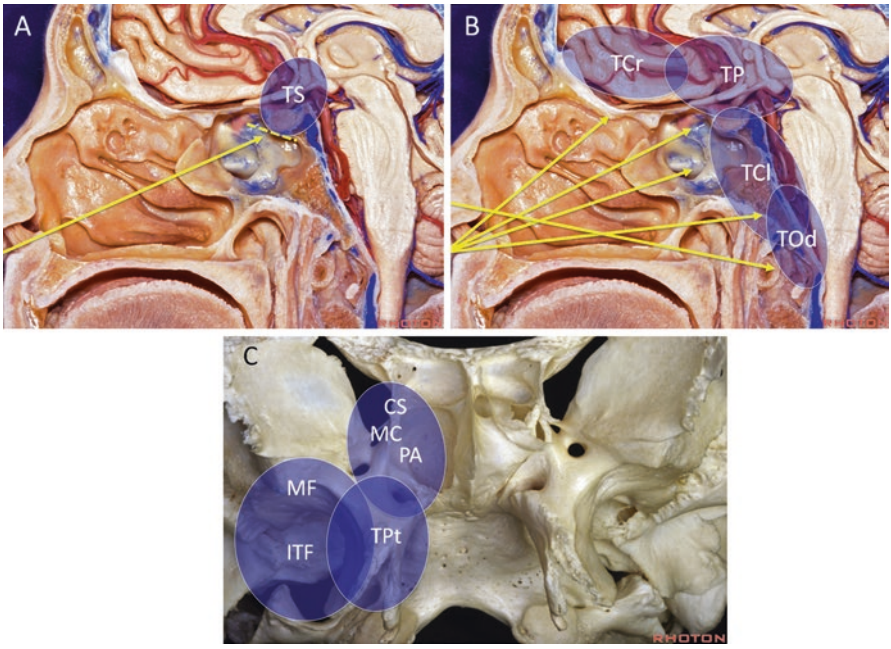

Fig. 17.1 (**a**) Sagittal cadaver prosection demonstrating the endoscopic endonasal transsellar (*TS*) corridor to the parasellar region. (**b**) Various extended endoscopic endonasal corridors to the skull base. *TCr* transcribriform, *TP* transplanum transtuberculum, *TCl* transclival, *TOd* transodontoid. (**c**) Coronal plane corridors demonstrated on a dry skull via the transpterygoid (*TPt*) approach. *MF* middle fossa, *ITF* infratemporal fossa, *CS* cavernous sinus, *MC* Meckel's cave, *PA* petrous apex (Courtesy of Rhoton Collection)

lesion. Above the level of the sphenoid floor, lesions of cribriform, anterior skull base, and suprasellar sites can be accessed via the transcribriform, transplanum transtuberculum, and transsellar corridors by removing the bone from the cribriform and fovea ethmoidalis, planum sphenoidale and tuberculum sellae, and sella turcica, respectively. Below the sphenoid floor, lesions of clivus, retroclival region, and craniocervical junction can be accessed via the transclival and transodontoid corridors by removing the bone from the clivus and the anterior arch of C1/odontoid process, respectively.

Transsellar Approach

The endoscopic endonasal transsellar approach, often considered the most basic of transsphenoidal variations, provides a panoramic view of the sella. Required steps to access this corridor include bilateral sphenoidotomies, removal of the rostrum of the sphenoid, posterior ethmoidectomies, a posterior septectomy, and a wide sellar bone opening. The resulting broad exposure provides the surgeon with a superior panoramic view of the sella, as well as an increased instrument maneuverability. The most critical anatomical structures of this approach, often colloquially referred as the "four blues," are the medial walls of the cavernous sinuses bilaterally and the superior and inferior intercavernous sinus in the rostrocaudal axis. This approach

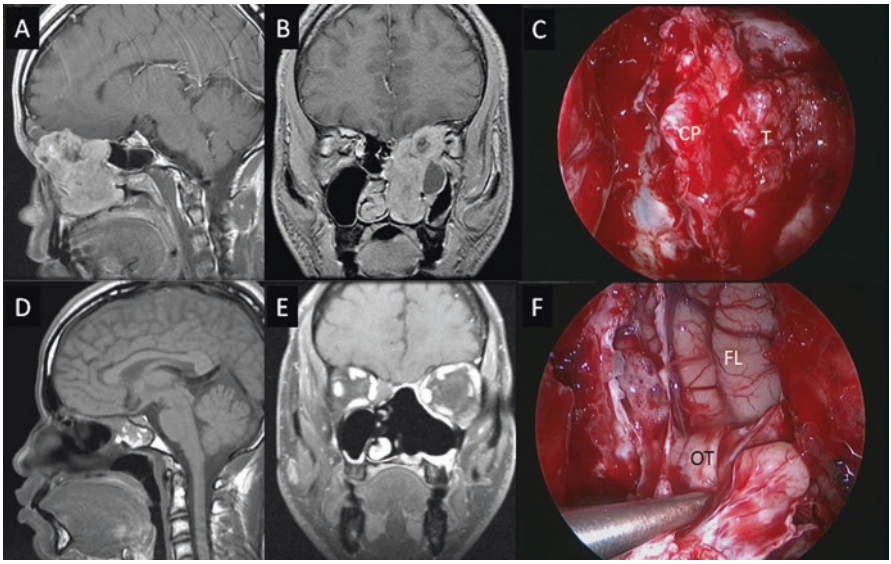

Fig. 17.2 Preoperative sagittal (**a**) and coronal (**b**) postgadolinium T1-weighted MRI showing an adenoid cystic carcinoma of the sinonasal cavity invading the left cribriform plate and left orbit. (**c, f**) The tumor (*T*) was removed using an extended endoscopic transcribriform transorbital approach (*CP* cribriform plate, *OT* olfactory tract, *FL* frontal lobe). (**d, e**) Postoperative MRI (**d**: sagittal, **e**: coronal) at 4 years after surgery and radiation therapy shows no evidence of tumor recurrence

alone is best suited for resection of intrasellar pathology such as pituitary adenomas and Rathke's cleft cysts. The transsellar corridor can be combined with a variety of other approaches depending on the extent of extrasellar disease involvement.

Transcribriform Corridor

The transcribriform corridor can be accessed with removal of the cribriform plate and fovea ethmoidalis (Fig. 17.2). The anatomical confines of this approach include the posterior table of the frontal sinus (anteriorly), the planum sphenoidale (posteriorly), and the lamina papyracea (laterally). The most important neurovascular structures are the anterior and posterior ethmoidal arteries. This approach is most commonly used for resection of midline olfactory groove meningiomas [13, 33], esthesioneuroblastomas, or other sinonasal malignancies (adenoid cystic carcinoma, adenocarcinoma, sinonasal neuroendocrine carcinoma, and sinonasal undifferentiated carcinoma) with extension into the anterior cranial fossa. Additionally, we have successfully used this approach for resection of olfactory schwannomas [34] and anterior skull base sinonasal osteoblastomas [35].

Transplanum Transtuberculum Approach

The transplanum transtuberculum corridor provides exposure to the suprasellar cistern [36], which can be accessed with resection of the planum sphenoidale and tuberculum sellae (Figs. 17.3 and 17.4). It is bordered anteriorly by the sphenoethmoidal junction, posteriorly by the anterosuperior border of the sella turcica, and laterally by the optic canals and paraclinoid internal carotid arteries. The medial

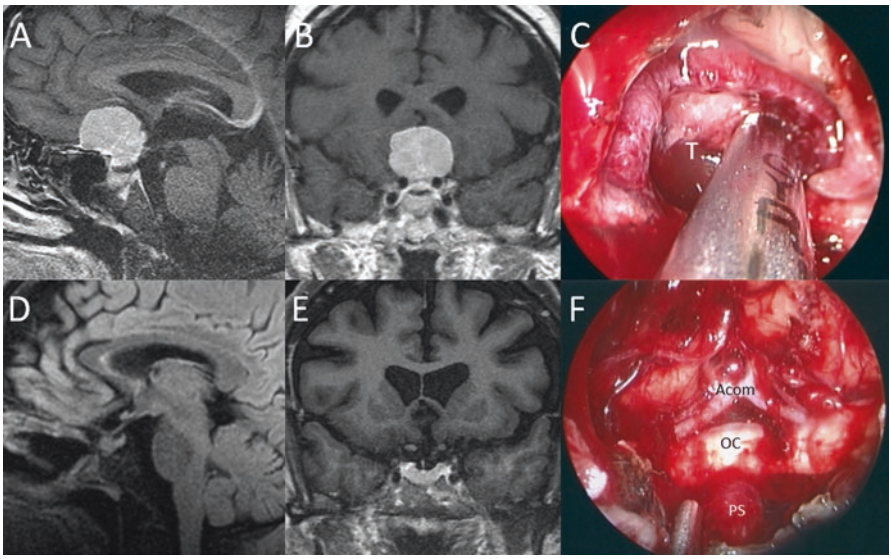

Fig. 17.3 (**a**, **b**) Preoperative postgadolinium T1-weighted MRI (**a**: sagittal view, **b**: coronal view) demonstrating a tuberculum sellae meningioma that was removed via the endoscopic endonasal transplanum transtuberculum approach. (c) Intraoperative photograph demonstrating central debulking of the tumor (*T*) with a microdebrider. (**d, e**) Postoperative postgadolinium T1-weighted MRI (**d**: sagittal view, **e**: coronal view) demonstrating complete removal of the tuberculum sellae meningioma without residual tumor. (**f**) Intraoperative photograph showing the final view of the resection bed after tumor removal with anterior communicating artery complex (Acom), optic chiasm (*OC*), and pituitary stalk (*PS*)

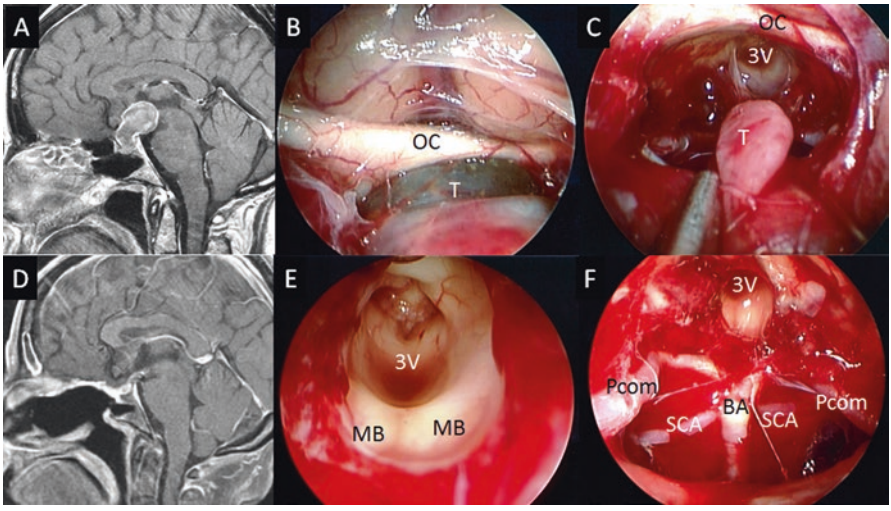

Fig. 17.4 (**a**) Preoperative postgadolinium T1-weighted MRI (sagittal view) showing a retrochiasmatic craniopharyngioma compressing the optic chiasm. (**b, c**) Endoscopic view of the tumor (*T*) in the suprasellar cistern and tumor removal from the retrochiasmatic space via the endoscopic endonasal transplanum transtuberculum approach. (**d**) Postoperative postgadolinium T1-weighted MRI (sagittal view) showing complete removal. (**e, f**) Endoscopic view of resection bed after tumor removal. *OC* optic chiasm, *3 V* third ventricle, *MB* mammillary body, *BA* basilar artery, *Pcom* posterior communicating artery, *SCA* superior cerebellar artery

opticocarotid recess is the principal structural landmark. It is a teardrop-shaped osseous indentation formed at the medial junction of the paraclinoid carotid canal and the optic canal. Dorsally, it has vertices at the inferior aspect of the lateral tuberculum crest, the medial aspect of the junction of the superior and posterior surfaces of the optic strut, and the superolateral aspect of the tuberculum [37]. This approach is best suited for resection of pituitary lesions with significant supradiaphragmatic extension, retrochiasmatic and suprasellar craniopharyngiomas [14, 38], and tuberculum sellae/planum sphenoidale meningiomas [13] that range from 2 to 3 cm in size. In the past, the use of transsphenoidal approaches for suprasellar lesions was generally limited to suprasellar lesions in which the sella turcica was enlarged. With the endoscopic transplanum transtuberculum approach, however, purely suprasellar lesions can be removed even when the sella turcica has a normal size [10, 13, 22, 25, 27, 39–42]. In these cases, the additional bony exposure enhances surgical maneuverability and provides improved visualization of the suprasellar portions of the tumor and reduces the amount of blind curettage in this region. Excellent results of craniopharyngioma excision via the transplanum transtuberculum route microsurgically have also been reported by Laws et al. [21, 25], Maira et al. [41, 42], and Couldwell et al. [27]. The transplanum transtuberculum corridor may not be suitable for cases that have significant lateral extension beyond its borders (lateral to optic nerves and carotid arteries). In these cases, a transcranial approach (frontotemporal, frontolateral, orbitozygomatic, or bifrontal transbasal) may be necessary.

Transclival Approach

The transclival approach is defined by partial or complete removal of the clivus to access extradural or intradural lesions (Fig. 17.5). Working through the corridor of the sphenoid sinus allows access to the upper two-thirds of the clivus, whereas working below the floor of the sphenoid provides access to the inferior one-third of the clivus and craniovertebral junction. When accessing the craniovertebral junction, a posterior septectomy plus removal of the rostrum and floor of the sphenoid bilaterally is needed. Alternative mucosal-sparing techniques to the conventional posterior bony and mucosal septectomy have been described for use when the mucosal integrity of the posterior nasal septum and preservation of the vascularized pedicled nasoseptal flap are desired [43]. The lateral anatomical confines of this corridor are defined by the cavernous and paraclival internal carotid arteries. Important landmarks include the dorsum sellae, the cavernous and paraclival segments of the internal carotid artery, the sixth nerves, and the hypoglossal canals. The critical neurovascular structures encountered through this approach are the oculomotor nerves bilaterally, the pituitary stalk, the mammillary bodies, the basilar artery, the P1 and P2 branches of the posterior cerebral arteries, the midbrain, and the pons. This approach is most commonly indicated for resection of extradural midline clival neoplasms such as chordomas and chondrosarcomas [27, 44–48], which may extend intradurally. Any extension into the sphenoid sinus and nasal cavity can be easily removed with the extended EEA. Additionally, this corridor provides direct exposure to the anterior surface of the brainstem, allowing access to lesions in this critical location without cerebral retraction [49]. As mentioned

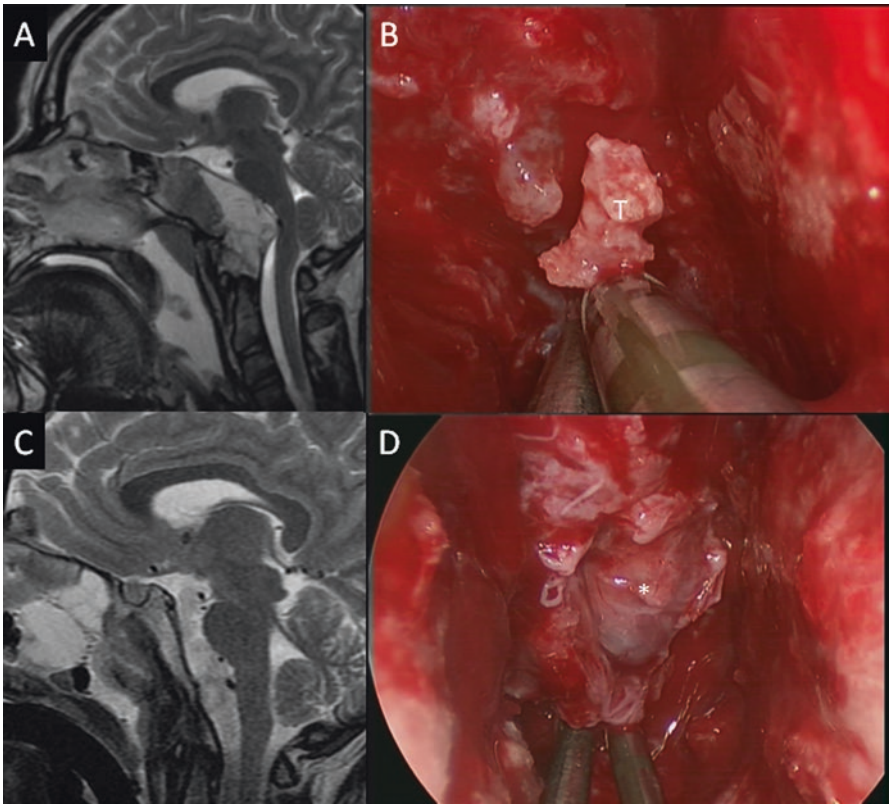

Fig. 17.5 (**a**) Preoperative sagittal T2-weighted MRI shows a clivus chordoma in the midline compressing the brainstem. (**b, d**) The tumor (*T*) was removed via endoscopic endonasal transclival approach. The dural defect (*) was visualized and repaired with a multilayered closure. (**c**) Postoperative sagittal T2-weighted MRI shows no evidence of recurrent chordoma

previously, the relative lateral limitations of this approach are the cavernous and paraclival carotid arteries. Larger lesions with significant lateral extension may require an open transcranial approach (petrosal, transmastoid transcervical, and far lateral) or combined approaches for their removal.

Transodontoid Approach

The endoscopic endonasal transodontoid approach is defined by removal of the C2 odontoid process (Fig. 17.6). It can be seen as caudal extension of the transclival approach, as it requires the same initial steps, namely a posterior septectomy (with/without mucosal sparing) and bilateral removal of the rostrum and floor of the sphenoid, plus an additional posterior and superior nasopharyngectomy with subsequent removal of the anterior arch of C1 and the odontoid process of C2. In some instances of basilar invagination, it may be necessary to remove the inferior aspect of the clivus to access the C1/2 complex. This transodontoid corridor extends coronally to

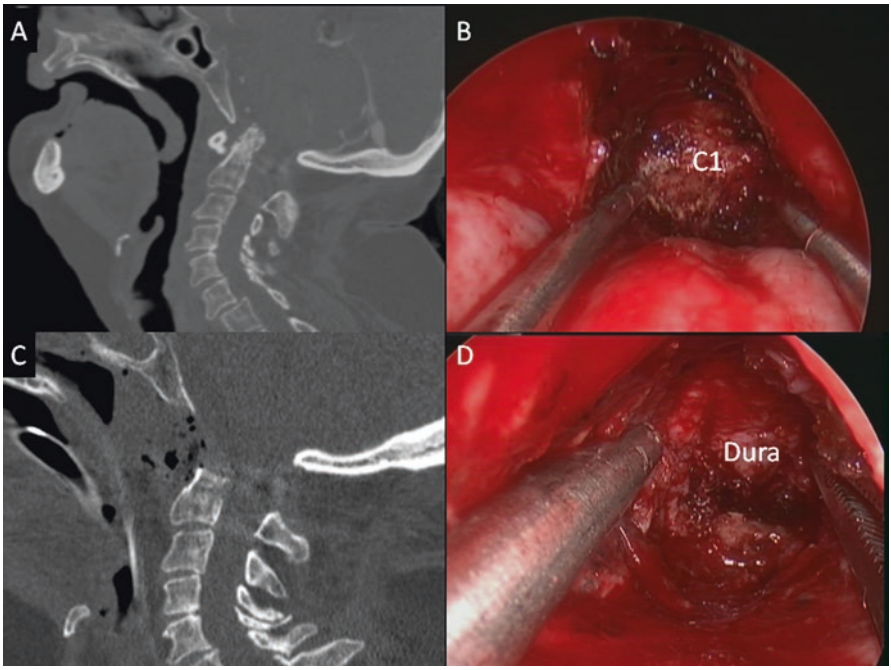

Fig. 17.6 (**a**) Preoperative sagittal CT scan shows basilar invagination and compression of the cervicomedullary junction. (**b, d**) Intraoperative photographs demonstrating the endoscopic endonasal transclival transodontoid approach. The C1 tubercle (*C1*) is drilled off, followed by removal of the odontoid process to expose the dura of the cervicomedullary junction. (**c**) Postoperative sagittal CT scan shows excellent decompression of the cervicomedullary junction after the endoscopic endonasal odontoidectomy

the lateral masses of C1, superiorly to the inferior clivus, and inferiorly down to the body of C2. Important landmarks include the Eustachian tubes, occipital condyles, and C1 lateral masses laterally. This approach is suited for lesions with extension below the inferior clivus, predominantly for abnormalities of the craniocervical junction requiring anterior decompression [50]. Irreducible basilar invagination, rheumatoid pannus, chordoma, and chondrosarcoma are typical indications for this approach, as long as their lateral extension remains within the aforementioned anatomical confines of this approach and does not spread beyond the vertebral arteries. The naso-axial line, which is drawn from the midpoint between the rhinion and the anterior nasal spine that extends toward the posterior edge of the hard palate and continues toward the craniovertebral junction, can help predict the inferior limit of the endonasal endoscopic approach to the craniovertebral junction [51]. In a study by Aldana et al. [52], the naso-axial line was more accurate than the nasopalatine line in predicting the inferior limit of exposure. In cases where lesions are found above the palatine line, the EEA is not just a viable option, but actually represents the preferred module of approach [50].

Coronal Plane Approaches

In the coronal plane, lesions with lateral extension into the infratemporal fossa, Meckel's cave, cavernous sinus, and petrous apex can be accessed endoscopically via the transpterygoid, transcavernous, and paraseptal corridors, respectively (Fig. 17.1c).

Transpterygoid Approach

The endoscopic endonasal transpterygoid approach (Fig. 17.7) is defined by the complete or partial removal of the pterygoid process. It was originally utilized to obtain surgical access to the lateral recess of the sphenoid sinus [53]; however, recent technological advancements in endoscopic technology have allowed this corridor to be extended to approach key structures of the skull base including the infratemporal fossa, petrous apex, Meckel's cave, and cavernous sinus. Regardless of the target being approached, required steps include attainment of a transmaxillary corridor, displacement or ablation of soft tissue within the pterygopalatine fossa (PPF), and removal of the pterygoid process. These approaches were initially

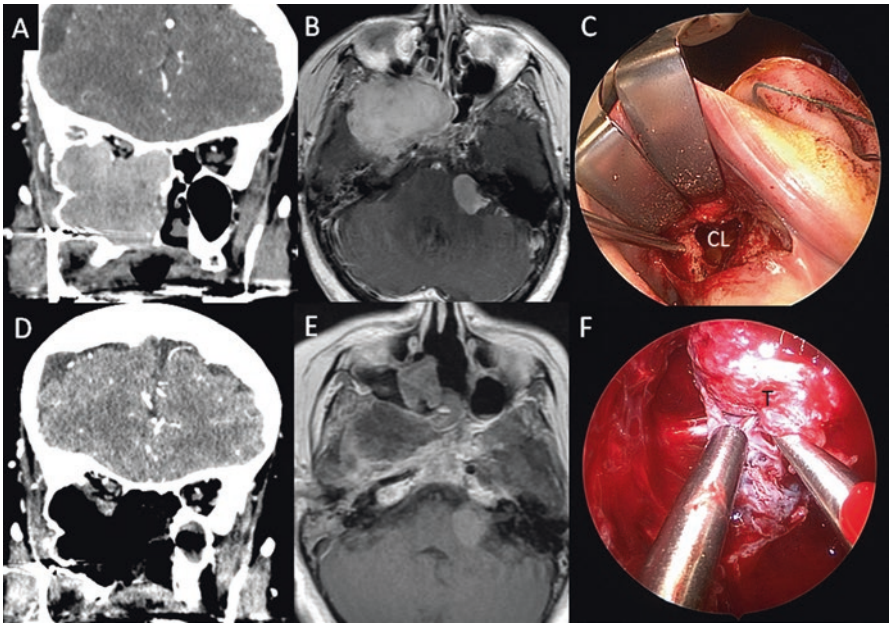

Fig. 17.7 Preoperative coronal CT angiogram (**a**) and axial postgadolinium T1-weighted MRI (**b**) demonstrating an extensive radiation-induced meningioma involving the infratemporal fossa and right nasal cavity. There was also a left cerebellopontine angle meningioma. (**c. f**) The infratemporal fossa tumor (*T*) was removed via a combined endoscopic endonasal transpterygoid and sublabial Caldwell-Luc (*CL*) maxillotomy approach. (**d, e**) Postoperative coronal CT (**d**) and axial postgadolinium T1-weighted MRI (**e**) shows complete resection of the infratemporal fossa meningioma

performed with a microscope, but the endoscope facilitates visualization through this corridor [54, 55]. The location and size of the lesion determine the dimensional needs of the corridor, which can be estimated by drawing imaginary horizontal and vertical lines through the foramen rotundum and vidian canal, respectively. These foramina represent the most critical landmarks of this approach. Important neurovascular structures in this region include the trigeminal nerve (V1–V3), the vidian nerve and artery, the internal carotid artery, and the internal maxillary artery and its branches [56].

The transpterygoid approach provides a multifaceted passage to deeper running corridors extending in the coronal plane of the skull base. Access to the infratemporal fossa, a region historically known for its difficult exposure, can be gained with this approach by variable removal of the pterygoid plates [32, 53]. This approach is designed for lesions extending below the vidian canal. Hence, antral access to this corridor requires a medial maxillectomy extending anteroposteriorly from the nasolacrimal duct to the posterior wall of the antrum and superoinferiorly from the inferior orbital wall to the floor of the nasal cavity [53]. According to the needs of the case, a Denker's approach can be combined with the endoscopic endonasal transpterygoid approach to gain greater exposure into infratemporal fossa and middle cranial fossa. Alternatively, a Caldwell-Luc maxillotomy via a sublabial incision can be performed instead of a Denker's approach to provide an additional corridor in combination with the binostril corridors to access the lateral infratemporal fossa [57]. The transpterygoid approach to the infratemporal fossa is suitable for accessing V3 schwannomas, extensive juvenile nasopharyngeal angiofibromas, meningiomas, adenoid cystic adenomas, and sarcomas.

Approach to the Petrous Apex

The petrous apex is the only target in the coronal plane that does not require access via an initial transpterygoid corridor. Because of its lateral position in relation to the sphenoid sinus and clivus, a paraseptal approach is often employed. This route is essentially a lateral extension of the transseptal/transclival approaches. Important landmarks and critical neurovascular structures include the vidian nerve, the carotid protuberance, and the abducens nerve as it is channeled from the pontine cistern to the cavernous sinus through Dorello's canal [53].

This approach to the petrous apex is especially suited for drainage of cholesterol granulomas (Fig. 17.8), as well as resection of clival chordomas and chondrosarcomas that extend laterally to the petrous apex. Lateral visualization in the trajectory of the petrous apex can be maximized by inserting the endoscope in the contralateral nostril or with the use of angled lenses [58]. This approach can be considered as an alternative to the traditional transpetrosal, subtemporal, or retrosigmoid approaches because it provides direct access to the petrous apex and creates the ideal path for drainage of cholesterol granulomas once marsupialized into sphenoid sinus [32].

Transcavernous Approach

The endoscopic endonasal transcavernous approach (Fig. 17.9) provides wide exposure to otherwise inaccessible structures located in the anterior upper one-third of the posterior fossa, namely the interpeduncular fossa, the prepontine cistern, and

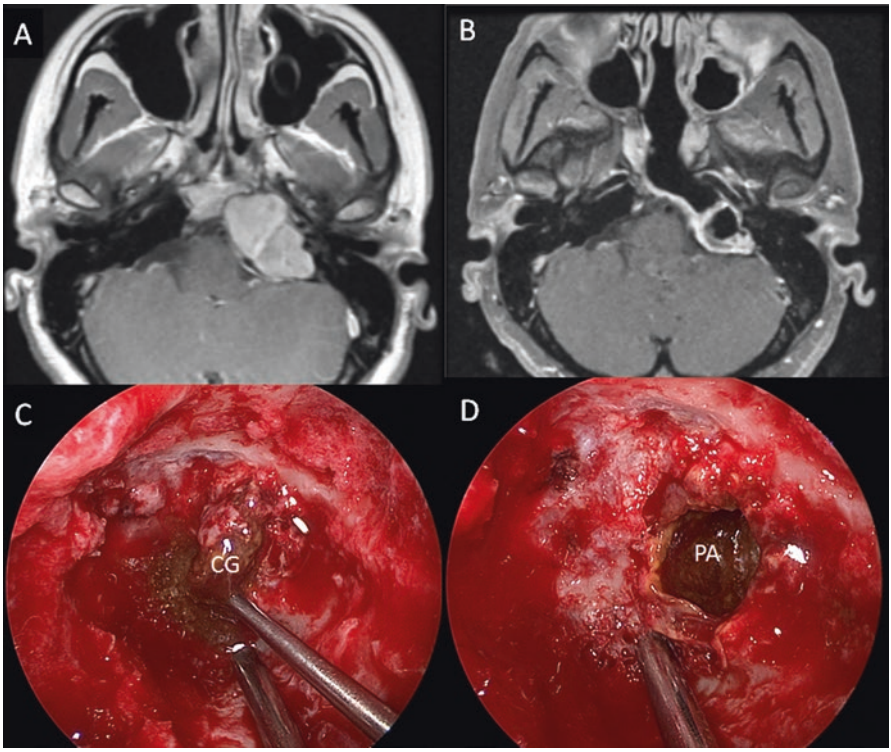

Fig. 17.8 (**a**) Preoperative axial postgadolinium T1-weighted MRI showing a left petrous apex cholesterol granuloma. (**b**) Postoperative axial postgadolinium T1-weighted MRI shows no evidence of recurrent cholesterol granuloma. (**c, d**) The lesion was fenestrated using an endoscopic endonasal approach to the petrous apex. The cholesterol granuloma (*CG*) is exposed and widely fenestrated. The petrous apex (*PA*) is identified after draining the contents of the granuloma

Meckel's cave (Fig. 17.10). This approach is best suited for pathologic entities with lateral extension beyond the sella turcica. These include pituitary tumors with lateral extension into the medial wall of the cavernous sinus and extradural lesions such as trigeminal nerve schwannomas within Meckel's cave. The development of this particular technique has enabled more complete resection of pituitary adenomas, thereby reducing the need for blind curettage of tumor performed by reaching into the cavernous sinus via the sella (medial to lateral approach). Additional bone over the carotid grooves can be unroofed, exposing the C3 portion of the internal carotid artery. The cavernous sinus is typically accessed by opening the dura just medial to the carotid artery. More recently, the indications for cavernous dissection in the setting of a pituitary tumor have been further reduced with the increased application of stereotactic radiosurgery. In cases where significant residual tumor is left in the cavernous sinus, we use this extended approach to transpose the pituitary away from the residual tumor and interpose a fat graft between the cavernous sinus and the gland (hypophysopexy) in preparation for planned adjuvant radiosurgery for the residual tumor in the cavernous sinus [59, 60]. This technique reduces radiation

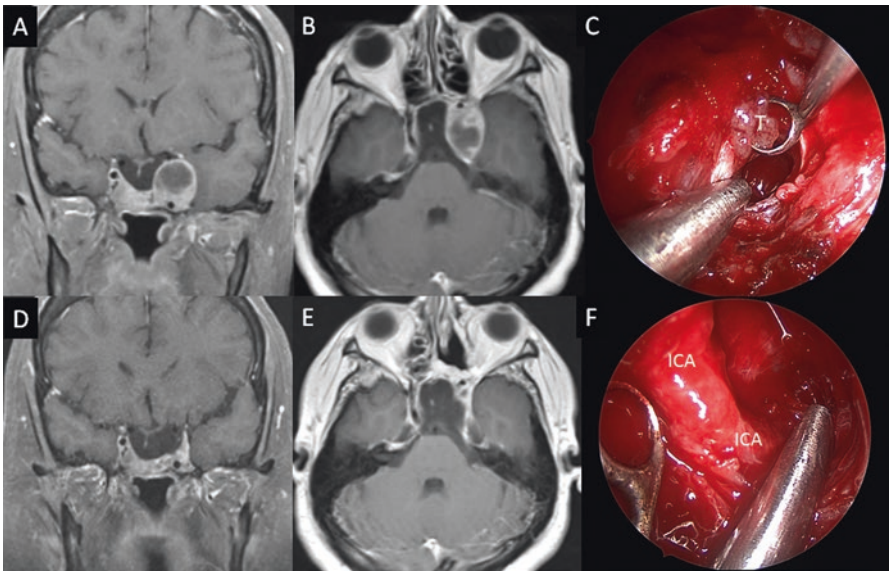

Fig. 17.9 (**a, b**) Preoperative coronal (**a**) and axial (**b**) postgadolinium T1-weighted MRI showing a left recurrent cavernous sinus pituitary adenoma causing a left sixth nerve palsy. (**c, f**) An endoscopic endonasal transcavernous approach was performed. The anterior corridor to the cavernous sinus was achieved lateral to the internal carotid artery (*ICA*). Gross total resection of the tumor (*T*) was performed. (**d, e**) Postoperative coronal (**d**) and axial (**e**) postgadolinium T1-weighted MRI shows no evidence of residual tumor. The left sixth nerve palsy improved after surgery

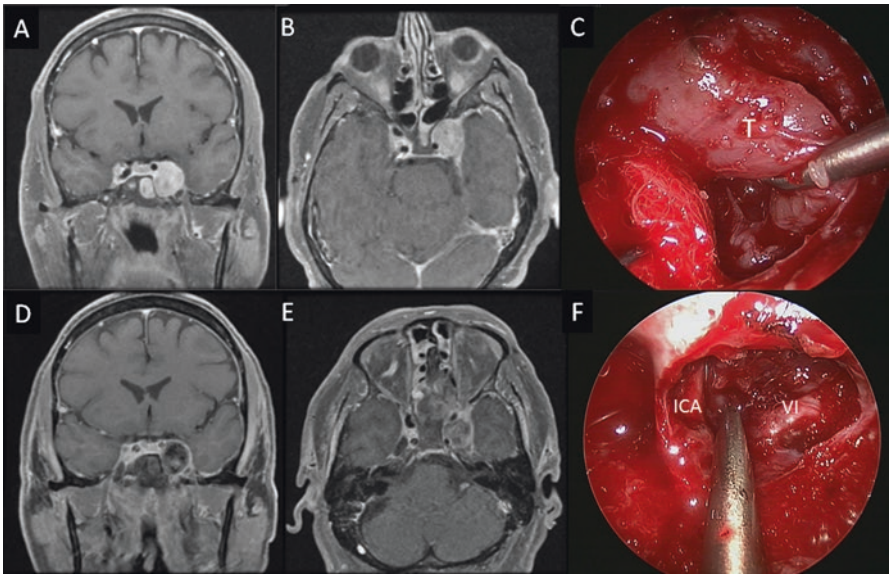

Fig. 17.10 (**a, b**) Preoperative coronal (**a**) and axial (**b**) postgadolinium T1-weighted MRI showing a left Meckel's cave schwannoma. (**c, f**) An endoscopic endonasal transpterygoid approach to Meckel's cave was performed. Gross total resection of the tumor (*T*) was performed. The left paraclival internal carotid artery (*ICA*) and left abducens nerve (*VI*) were visualized in the resection bed. (**d, e**) Postoperative coronal (**d**) and axial (**e**) postgadolinium T1-weighted MRI shows no evidence of residual tumor

exposure to the pituitary gland to minimize the risk of hypopituitarism. Tumors that extend laterally into the cavernous sinus may be visualized by placing an angled endoscope into the sella. An extended EEA lateral to the internal carotid artery can also be performed to directly remove cavernous sinus tumors that present or extend lateral to the internal carotid artery.

Operative Techniques

Patient Positioning

The patient is placed supine on the operating table with the head placed in 3-pin fixation. The head is rotated slightly toward the right side to facilitate binostril access for two surgeons that stand on the patient's right side. Slight elevation of the head of the bed or reverse Trendelenburg positioning can help minimize cavernous sinus venous pressure and bleeding while facilitating venous return. Slight flexion allows visualization of lesions that extend inferiorly along the clivus and craniocervical junction. Extension of the head allows visualization of lesions with suprasellar extension and exposure of the cribriform region (Fig. 17.7). In the case of ventral decompression of the cervicomedullary junction (transodontoid approach), securing the patient's head in a Mayfield 3-pin fixation system and application of gentle traction to the head holder in the neutral position are preferred because flexion or extension of the patient's head may result in worsening the compression of the brainstem or spinal cord [51]. Below we provide an overview of operative techniques according to surgical approach.

Sagittal Plane Approaches

Transsellar Approach

In the standard microscopic transsphenoidal transsellar approach (Fig. 17.1a), the sella can be exposed with either a sublabial submucosal or a direct endonasal approach as described elsewhere [6, 12, 26, 28, 61]. In the case of microscopic resection, a bivalve speculum is placed, and the rostrum of the sphenoid sinus is exposed and opened to visualize the sellar floor. The sphenoid sinus mucosa is exenterated and the sellar floor is removed with a high-speed drill and Kerrison rongeurs to expose the sellar dura.

If an EEA is planned, we use a multidisciplinary team approach comprising a skull base neurosurgeon working simultaneously with an otolaryngologist specializing in endoscopic sinus and skull base surgery. We use a binostril (binarial) technique without the aforementioned nasal speculum. Both surgeons work simultaneously with three to four instruments in the field at a time. The initial endonasal exposure to the sphenoid sinus is performed by the otolaryngologist using a 4-mm diameter, 18-cm-long, 30° endoscope (Karl Storz, Tuttlingen, Germany). We prefer to use a 30° endoscope for the exposure and resection (unlike the 0°

endoscope reported by most authors) because it provides the same degree of surgical exposure but with the versatility of additional angled viewing capabilities around the corners, without having to repeatedly exchange the two endoscopes. The middle and inferior turbinates are lateralized with a Goldman elevator. The sphenoid sinus and sphenoid ostia are identified approximately 1.5 cm above the choanal arch. A wide bilateral sphenoidotomy is followed by bilateral posterior ethmoidectomies and a posterior septectomy. The resulting cavity creates an adequate working space for multiple endoscopic instruments to be inserted into both nostrils, which are triangulated at the deep surgical target. Once the endoscope is advanced into the sphenoid cavity, the surgeon is presented with a superior panoramic view of the sellar floor and surrounding structures including the tuberculum sella and planum sphenoidale anteriorly, the opticocarotid recesses and paraclival arteries laterally, and the clival recess and floor of the sphenoid sinus inferiorly. The sellar floor is removed widely with a high-speed drill and Kerrison rongeurs until the medial margins of the cavernous sinus and the margins of the superior and inferior intercavernous sinus are exposed. The dura is opened widely with an arachnoid knife and extended with angled pistol-gripped microscissors to access the sellar tumor.

Transcribriform Approach

The endoscopic endonasal transcribriform approach is suitable for sinonasal malignancies involving the cribriform plate, such as esthesioneuroblastomas, and also for select olfactory groove meningiomas where anosmia is already present (Fig. 17.2). The approach involves removal of both middle turbinates, a wide sphenoidotomy, anterior and posterior ethmoidectomies, and a wide Draf III (modified Lothrop) frontal sinusotomy. This is usually sufficient for benign tumors of the anterior skull base, such as olfactory meningiomas and schwannomas. For sinonasal malignancies, maxillary antrostomies are performed on the affected side(s) to prevent iatrogenic sinusitis and for exposure of the orbital floor as a major anatomical landmark [62]. A large vascularized pedicled nasoseptal flap is harvested and placed into the posterior nasopharynx until the time of closure [63]. Care is taken to harvest from the side that is devoid of tumor invasion. A superior septectomy is necessary to facilitate binostril triangulation of instrumentation for targeting the cribriform region. It is important to expose the junction of the lamina papyracea with the fovea ethmoidalis.

The cribriform plate is then resected using a high-speed diamond drill with copious irrigation. The margins of the bony removal are determined based on the extent of the lesion using neuronavigation. The posterior margin of resection is typically at the sphenoethmoidal junction while the anterior margin is at the posterior frontal sinus wall at the level of the crista galli. The fovea ethmoidalis is unroofed bilaterally. During the cribriform resection, the anterior and posterior ethmoidal arteries are ligated and divided to facilitate early devascularization of the tumor. Care is taken to avoid retraction of the arteries into the orbit so as to avoid a postoperative orbital hematoma. Both lamina papyracea should be removed in cases of sinonasal malignancies.

In patients with smaller unilateral lesions, exposure is performed in a similar fashion but with sparing of the contralateral sinonasal tissue and bony skull base. A modified subtotal Lothrop procedure may be performed for exposure of the frontal sinus (anterior limit of exposure) instead of the standard modified Lothrop procedure [63–65].

The dura of the anterior skull base is opened in a rectangular fashion to expose the underlying pathology. We typically open the dura laterally on both sides of the fovea ethmoidalis region in a longitudinal fashion. The transverse incision is made anteriorly with transection of the falx cerebri from an anterior to posterior fashion. The dura is then reflected posteriorly to expose both olfactory tracts, which are divided. The final cut is made transversely across the dura of the planum sphenoidale. At this juncture, the intradural tumor can be dissected carefully from the frontal lobes.

Transplanum Transtubercular Approach

Access to lesions in the suprasellar cistern, such as craniopharyngiomas and tuberculum sellae meningiomas, can be achieved through an endoscopic transplanum transtuberculum (extended transsphenoidal) approach (Figs. 17.3 and 17.4). To prevent a postoperative cerebrospinal fluid (CSF) leak, a pedicled nasoseptal flap is harvested during the endonasal exposure and placed inferiorly into the posterior nasopharynx for later use at the time of closure. As in the transsellar exposure, the sellar floor is removed, and then the bone over the planum sphenoidale and tuberculum sellae is carefully removed with a high-speed drill with copious irrigation. Once the bone is eggshell thin, an up-angled 5-0 curette is used to outfracture the bone to expose the underlying dura. We recommend removing the bone of the lateral tubercular strut so that the medial optic canals are decompressed. This facilitates exposure of the distal dural ring and control of the internal carotid artery as it enters the subarachnoid space. In cases of tuberculum sellae meningiomas, we also prefer to unroof both bony optic canals to decompress both optic nerves extradurally. The dural sleeves can then be opened selectively to remove any meningioma extending into the optic canals during intradural tumor removal. Care is taken not to injure either the optic nerves or the C3 carotid arteries during the bony removal. The horizontal incision is made in the planum dura and sellar dura above and below the superior intercavernous sinus, respectively. The dura is then extended vertically in the midline toward the superior intercavernous sinus. The sinus is then coagulated with a pistol-gripped bipolar cautery and divided sharply. The incision is carried along the diaphragm sella to expose the suprasellar cistern while preserving the pituitary gland in its position. At this point, the underlying lesion is further exposed and removed. With the angled endoscope, this approach enables an unencumbered view of the suprasellar cistern, retrochiasmatic space, third ventricle, and interpeduncular cistern.

Transclival and Transodontoid Approaches

For standard transclival exposure of clivus lesions, a wide sphenoidotomy, a posterior ethmoidectomy, and a posterior septectomy are performed in a similar fashion

as previously described in the transsellar approach (Fig. 17.5). Access through the sphenoid sinus provides exposure to the upper third (dorsum sellae to the sellar floor) and middle third (sellar floor to sphenoid floor) of the clivus. For exposure of the inferior third (sphenoid floor to foramen magnum), the mucosa over this portion of the clivus is incised and the mucosal flaps are mobilized laterally [43, 66, 67]. The posterior septectomy is extended inferiorly to the hard palate to optimize exposure to the lower clivus. The vidian nerve can be identified at its canal within the floor of the sphenoid sinus and followed posteriorly to locate the junction of the paraclival carotid artery and horizontal petrous carotid artery. It is important to identify the course of the internal carotid artery, Dorello's canal, and the hypoglossal canal in each patient so as to avoid possible neurovascular injury. Access to the upper clivus may require resection of the dorsum sellae and posterior clinoid processes. Primary bony tumors of the clivus are generally extradural but may invade intradurally in some cases. One should be prepared for multilayered reconstruction with a vascularized pedicled nasoseptal flap if there is an intraoperative CSF leak. A fat graft placed over the clival defect prior to flap placement is recommended to avoid delayed herniation of pontine encephaloceles.

Further access to the odontoid process can be achieved with a midline pharyngeal incision over the C1 tubercle between the two Eustachian tubes (Fig. 17.6). The mucosa and muscular soft tissue are mobilized and resected laterally to expose the anterior arch of C1. The C1 tubercle is removed with a high-speed drill to expose the underlying odontoid process. It is important to delineate the peripheral edges of the odontoid process and the base of the odontoid where it meets the body of C2. The odontoid process is hollowed out with a high-speed drill. The remaining thin, eggshell remnant of the bone is carefully dissected away from the soft tissue and dura with a 5-0 up-angled curette. The transverse ligament and the remaining soft tissue pannus are carefully resected and debulked until the underlying dura is visible. Expansion of the dural sac at the craniovertebral junction generally reflects adequate decompression. Care is taken to avoid a durotomy and subsequent intraoperative CSF leakage during endonasal endoscopic odontoidectomy procedures for basilar invagination.

Coronal Plane Approaches

Transpterygoid Approach

The endoscopic endonasal transpterygoid approach represents a common first step of most coronal plane approaches to the lateral skull base. The approach begins with resection of the uncinate process, identification and posterior widening of the maxillary ostium, and resection of the ethmoid bulla, suprabullar cells, and posterior ethmoid cells. This transethmoidal approach permits access to the sphenoid sinus, which is subsequently widened to allow maximal exposure and permit optimal instrument maneuverability within the sinus. Resection of the ipsilateral middle

turbinate may be necessary to provide an unobstructed exposure of the target. We recommend harvesting a pedicled nasoseptal flap prior to enlarging the sphenoid sinus inferiorly to avoid inadvertent injury to the vascular pedicle. Next, access to the PPF is gained by elevation and removal of the posterior-medial wall of the maxillary sinus. The orbital process of the palatine bone is removed to allow further visualization of the PPF. We lateralize the neurovascular contents of the PPF to expose important landmarks, such as the vidian nerve and the lateral wall of the sphenoid sinus, and to permit complete dissection of the sphenoid process of the palatine bone as well as the medial pterygoid plate. For this step, we prefer using a high-speed drill or Kerrison rongeurs. Successful drilling through the pterygoid process provides a wide exposure to the lateral recess of the sphenoid sinus and subsequent access to the medial aspect of the infratemporal fossa and middle cranial fossa [57, 68, 69]. For larger tumors involving the infratemporal fossa and middle cranial fossa, a medial maxillectomy and sublabial Caldwell-Luc maxillotomy are useful adjuncts in widening the corridors of exposure and increasing surgical freedom (Fig. 17.7).

Approach to the Petrous Apex

This approach can be viewed as a lateral extension of the midclival approach. The EEA can be considered when the tumor has created a corridor in the coronal plane via medial expansion into the sphenoid sinus. For this approach, we recommend wide bilateral sphenoidotomies with exposure of the clival recess via adequate drilling through the floor of the sphenoid sinus. Finally, access to the petrous apex can be gained by decompressing and lateralizing of the anterior genu and the paraclival internal carotid artery, a process requiring careful dissection of its surrounding bone encasement. Alternatively, one can access lesions behind the paraclival carotid artery with angled endoscopes and instrumentation without unroofing and transposing the artery (Fig. 17.8).

Transcavernous Approach

Parasellar tumors with lateral extension into the cavernous sinus can be accessed via the EEA. In general, softer tumors such as pituitary adenomas, schwannomas, and chordomas are more favorable to remove than meningiomas (Fig. 17.9). Access into the cavernous sinus can be achieved from a medial-to-lateral approach from the pituitary fossa. This is essentially a transsellar approach to remove, for example, a pituitary tumor in the midline sella that extends laterally into the cavernous sinus. The tumor can be followed into the cavernous sinus using an angled endoscope and curved suctions. Alternatively, an anterior approach can be performed by incising the periosteal dura over the cavernous sinus for direct anterior access. Care is taken to avoid injury to the cavernous carotid artery by mapping out the course of the artery using micro-Doppler sonography and image guidance. In general, we recommend removing only what is soft and readily aspirated with suction. Anything that is firm or fibrous should be left behind for stereotactic radiosurgical treatment to avoid potential cranial nerve injury. Vascular injury can be caused if the surgeon does not recognize deviations in the course of the carotid arteries, such as an ectatic

carotid artery that underlies the sellar dura. In some cases, it may be useful to include the ipsilateral neck in the prepared field for proximal control of the carotid artery, in the event of significant carotid artery hemorrhage that may not be controlled by local hemostatic maneuvers.

When performing transcavernous access, the dura underlying the sellar floor is exposed in the same manner as described previously in the transsellar approach. The bony removal is extended laterally to expose the cavernous sinus, including the dura overlying the carotid artery. This can be extended toward the lamina papyracea, if needed. In addition, more inferolateral exposure of the superior orbital fissure, foramen rotundum, and the paraclival carotid artery can be performed by adding an ipsilateral transpterygoid approach. After the bony removal, the sellar dura is opened sharply in the midline and extended with angled scissors. The tumor is removed with suction and curettes, and the tumor can be followed laterally into the cavernous sinus using angled endoscopes and instrumentation (Fig. 17.9). Care is taken to carefully visualize the cavernous carotid artery to avoid injury. The superior compartment of the cavernous sinus (located superior to the horizontal segment of the cavernous carotid artery) is readily accessed with this approach. Alternatively, an anterior approach can be performed to the lateral compartment of the cavernous sinus. After the course of the internal carotid artery is mapped out with micro-Doppler and image guidance, an incision is made with an arachnoid knife or number 11 blade in a safe zone devoid of the cavernous carotid artery. The incision is extended with angled scissors to access the lateral compartment. Tumor is removed in the standard fashion with suction and curettes. Any venous bleeding can be controlled by gentle packing with Surgicel or Gelfoam, with care not to compress the cavernous cranial nerves.

Reconstruction

Independent of the selected approach, after tumor removal, the dural defect must be repaired carefully. In the absence of an intraoperative CSF leak, the defect can be covered with a piece of acellular dermal allograft after filling the dead space with Gelfoam. However, in the presence of an intraoperative CSF leak, the authors prefer to use a multilayered closure with autologous fascia lata or acellular dermal allograft, followed by a vascularized pedicled nasoseptal flap [62, 63, 68–71]. For transcribriform defects, we typically use a triple-layered reconstruction technique composed of an initial acellular dermal allograft inlay, a second acellular dermal allograft overlay that is wedged underneath the bone edge with Gelfoam, followed by a final nasoseptal flap layer (Fig. 17.11). For transplanum defects, we typically use two layers of autologous fascia lata as an overlay followed by the nasoseptal flap (Fig. 17.12). For transclival defects, we use an autologous fat graft placed into the clival defect prior to flap placement to prevent pontine herniation. After final positioning of the nasoseptal flap over the bony skull base defect, the flap is secured in place with a layer of Surgicel and bolstered with gentamicin-soaked Gelfoam pledgets followed by a Merocel pack (Medtronic Xomed, Jacksonville, FL, USA). We

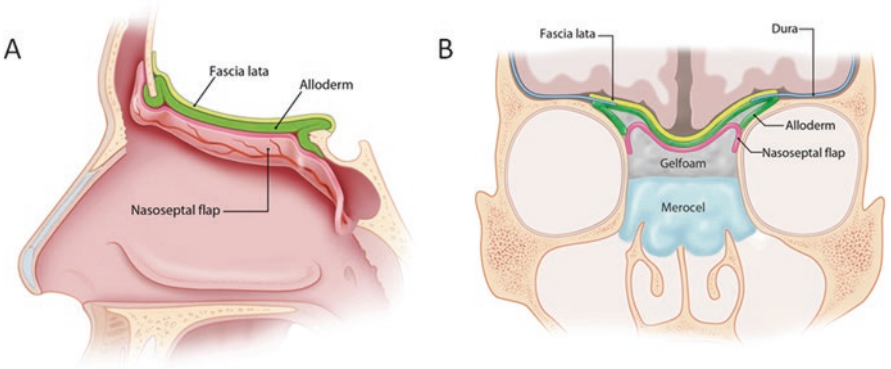

Fig. 17.11 (**a**) Diagram demonstrating repair technique of skull base defect after transcribriform approaches using triple-layered reconstruction with autologous fascia lata, alloderm, and a vascularized pedicled nasoseptal flap. (**b**) The repair is bolstered with gentamicin-soaked Gelfoam pledgets and a Merocel pack (Copyright Chris Gralapp, with permission)

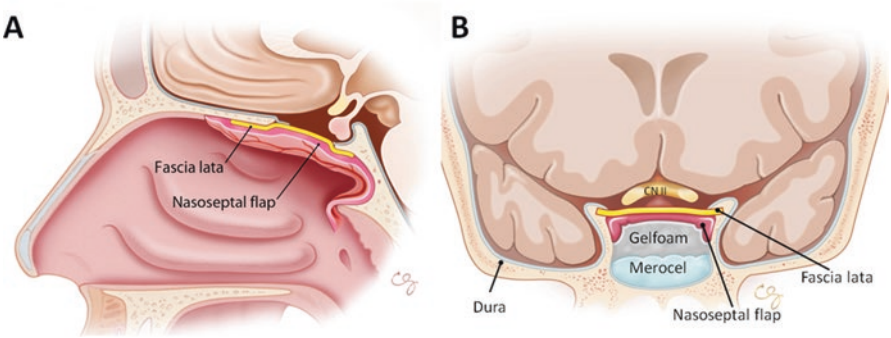

Fig. 17.12 (**a**) Diagram demonstrating repair technique of skull base defect after transplanum transtuberculum approaches using multilayered reconstruction with autologous fascia lata and a vascularized pedicled nasoseptal flap. (**b**) The flap is bolstered with gentamicin-soaked Gelfoam pledgets and a Merocel pack (Copyright Chris Gralapp, with permission)

do not use dural sealants because leakage of these materials between the dural closure and the nasoseptal flap may prevent flap adherence. Additionally, a recent retrospective review at our institution analyzing dural repair with or without sealant found no significant difference in the rate of postoperative CSF leak between the two groups [68]. The Merocel packing is left in place for about 10–12 days after surgery, and the patient is maintained on antibiotics until the packs are removed. Because the patient is already in a CSF hypovolemic state at the end of surgery, we typically do not use postoperative lumbar drainage so as to avoid complications of CSF hypotension except in transplanum and transclival cases where there is a higher flow leak from larger CSF cisterns [70, 72]. Absence of a lumbar drain allows the patient to recover more quickly and mobilize sooner, thus avoiding thromboembolic and pulmonary complications.

Complications

The most significant complications from the use of the extended and parasellar transsphenoidal approaches are CSF leak and vascular injury to the cavernous carotid artery and injury to the cavernous cranial nerves. The risk of CSF leakage may be reduced by careful multilayered reconstruction and use of a vascularized pedicled nasoseptal flap, with or without postoperative lumbar drainage. The increased use of the vascularized pedicled nasoseptal flap for endoscopic repair of skull base defects has significantly reduced the rate of postoperative CSF leaks in endoscopic skull base surgery. If a postoperative CSF leak is detected, we recommend early endoscopic re-exploration to investigate the source and site of leakage with subsequent revision of the reconstruction. These leaks are usually due to flap or graft migration or flap dehiscence. In cases of occult intracranial hypertension, a permanent CSF shunt may be required prior to definitive flap reconstruction.

To avoid intraoperative vascular injury, one must study the course of the internal carotid artery on preoperative CT angiogram images. This modality can also be used intraoperatively for image guidance. Additionally, a micro-Doppler ultrasonic device may be used intraoperatively to pinpoint the location of the carotid artery throughout the case. In some instances, it may be necessary to expose the ipsilateral cervical carotid artery in the neck for proximal control. If hemorrhage from the cavernous carotid artery occurs, it is usually controllable with packing of the rupture site with harvested crushed autologous muscle followed by cottonoids. However, failure to control the hemorrhage may necessitate ligation of the cervical carotid artery. Immediate postoperative angiography is performed to exclude the presence of a pseudoaneurysm, which may result in delayed, fulminant epistaxis, a potentially life-threatening condition. If a pseudoaneurysm is present, endovascular techniques are used to obliterate the lesion or occlude the carotid artery after a negative balloon occlusion test. If no pseudoaneurysm is noted on the immediate postoperative study, then delayed angiography is performed (7–10 days later) to rule out the occurrence of a delayed pseudoaneurysm.

Combined Transcranial and Endoscopic Endonasal Approaches

Lesions that extend beyond the zones of exposure of the extended endoscopic endonasal approaches may necessitate a combined approach (using another skull base approach in addition to the EEA) for adequate exposure and control of neurovascular structures. We have used this strategy for skull base lesions that occupy anatomical regions that are beyond the safe reach of the pure EEA.

For extensive lesions of the anterior skull base and paranasal sinuses with marked intracranial extension, we have used the endoscopic endonasal transcribriform approach in combination with the transbasal approach (Fig. 17.13) [19, 67]. The transbasal approach allows better visualization and neurovascular

control of the entire floor of the anterior skull base, orbital roofs, interhemispheric fissure, and suprachiasmatic regions. In addition, the pericranial flap from above can be used in conjunction with the nasoseptal flap from below ("double flap") [73], particularly in cases of malignancy where postoperative radiation therapy is anticipated (Fig. 17.14).

For extensive lesions of the infratemporal fossa, such as giant juvenile nasopharyngeal angiofibromas with intracranial and sinonasal involvement, we have also used a frontotemporal or orbitozygomatic approach in conjunction with a combined endoscopic endonasal and sublabial transmaxillary (Caldwell-Luc) approach [57]. This strategy allows multiportal, multicorridor access to multiple compartments with safe control of the cavernous internal carotid artery. Combined approaches can be performed in a single stage or in multiple stages depending on each scenario.

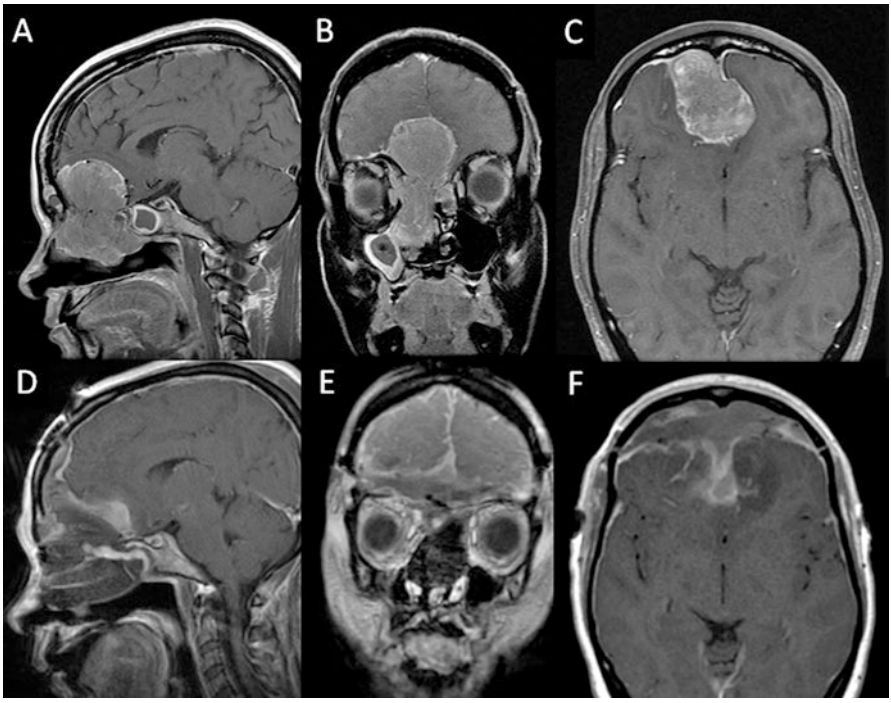

Fig. 17.13 (**a–c**) Preoperative postgadolinium T1-weighted MRI (**a**: sagittal, **b**: coronal, **c**: axial) of a large esthesioneuroblastoma involving the sinonasal cavity with significant intracranial invasion. The tumor was removed completely via a combined transbasal and endoscopic endonasal approach. Reconstruction of the skull base defect was performed using the double flap technique. (**d–f**) Postoperative postgadolinium T1-weighted MRI (**d**: sagittal, **e**: coronal, **f**: axial) shows no evidence of residual tumor

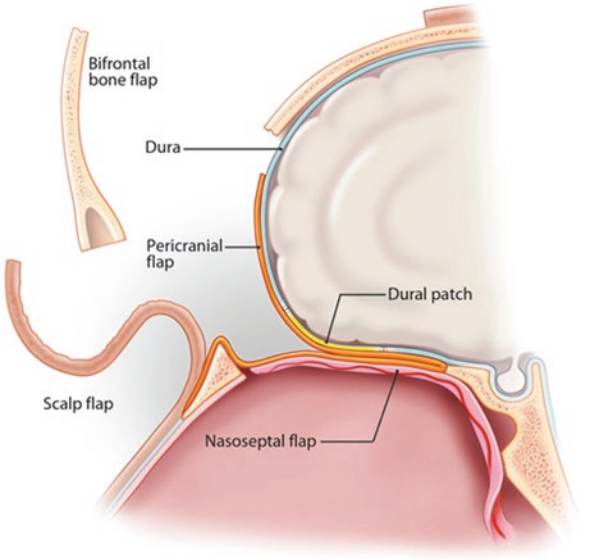

Fig. 17.14 Diagram demonstrating double flap repair technique after combined transcranial and endoscopic endonasal approaches. The anterior skull base defect is repaired with a pericranial flap from above and augmented simultaneously with a nasoseptal flap from below (Copyright Chris Gralapp, with permission)

Conclusions

Skull base approaches facilitate exposure of basal lesions by the removal of osseous structures to minimize brain retraction. The endoscopic transsphenoidal approach and its extended variations provide safe and useful alternatives for resecting midline skull base lesions involving the cribriform, tuberculum sellae, suprasellar region, cavernous sinus, and clivus/craniocervical junction. The extended EEAs can also be applied in the coronal plane to remove lesions in the infratemporal fossa, middle fossa, Meckel's cave, and petrous apex. These approaches can be used alone or in combination with other cranial base approaches depending on the location of the lesion. Complications can be minimized with appropriate patient selection, knowledge of the microsurgical and endoscopic anatomy, and surgical experience of a multidisciplinary skull base team.

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Closure Methods Following Transsphenoidal Surgery

18

Paul A. Gardner, Carl H. Snyderman,
Juan C. Fernandez-Miranda, and Eric W. Wang

Introduction

Cerebrospinal fluid (CSF) leak is one of the most common postoperative complications following endonasal surgery. The rate varies with defect location, tumor type, reconstruction technique, surgeon experience, and patient factors. CSF leak rates range from 1.5 to 5% for pituitary adenomas [1] to 10 to 16% for craniopharyngiomas and meningiomas [2, 3].

The severity of intraoperative CSF leak also correlates with the risk of postoperative leak. While this relationship is intuitive, classifying the severity can be challenging. One of the most widely used systems is that developed by Kelly in which intraoperative leaks are divided into three grades: Grade 1 is a small leak without obvious diaphragmatic defect, Grade 2 a moderate leak, and Grade 3 a large diaphragmatic/dural defect [4].

In addition to tumor factors and defect size, patient factors play a role in healing and rates of postoperative leak and therefore reconstruction used. Body mass index (BMI) is one of the most significant factors, with a quantifiable impact on postoperative leak rates [5]. Obesity clearly leads to an increase in intracranial pressure

Electronic supplementary material: Supplementary material is available in the online version of this chapter at 10.1007/978-3-319-56691-7_18. Videos can also be accessed at http://www.springerimages.com/videos/978-3-319-56689-4.

P.A. Gardner, MD (✉) • J.C. Fernandez-Miranda, MD
Department of Neurological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
e-mail: gardpa@upmc.edu

C.H. Snyderman, MD, MBA
University of Pittsburgh School of Medicine, Otolaryngology and Neurological Surgery, Pittsburgh, PA, USA

E.W. Wang, MD
University of Pittsburgh School of Medicine, Otolaryngology, Pittsburgh, PA, USA

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_18

and is implicated in diseases like pseudotumor cerebri and occult intracranial hypertension with spontaneous CSF leak. There are several hypotheses to explain this association, ranging from venous hypertension related to poor cranial outflow to hormonal impacts related to the increase in estrogens seen in obesity.

Other patient or tumor factors that impact healing and reconstruction include diabetes mellitus and inhibited healing in Cushing's disease, obstructive sleep apnea in acromegaly, and prior radiation for attempted tumor control. All of these potentially increase the risk of CSF leak/fistula and should lead to consideration of a more robust reconstruction.

There are a wide range of reconstruction techniques and materials used, all with a relatively high degree of success. There are, however, two generally accepted concepts that are widely applied for sellar and parasellar reconstructions: multilayer reconstruction and vascularized reconstruction. How these are applied and when depend largely upon the factors listed above.

Multilayer Reconstruction

Multilayer reconstruction has been used in the skull base and sella for decades. Autologous fat graft is the most common material used as a primary layer and often can be used in isolation following tumor resection without intraoperative leak or for low-flow leaks. Filling the sella or sphenoid with adipose tissue following pituitary tumor resection remains a popular technique, though it may lead to some chronic crusting and even mucocele if all underlying mucosa is not carefully stripped.

For higher flow leaks, fat is often "dumbbelled" into the defect, with a portion of it physically occupying the space previously filled with tumor. This technique seems to dramatically decrease the risk of postoperative leak, but should be used thoughtfully and with caution, as the fat is replacing the mass that was removed due to optic compression, and there are multiple reports of repeat surgery for fat removal due to new postoperative visual compromise. In addition, there are likely cases whereby this technique may have limited visual recovery, something that cannot be easily quantified.

An equally simple and effective technique is the use of free mucosal grafts to cover the sella. This is preferred due to its local, intranasal source and rapid healing. Mucosal grafts can be harvested from a resected middle turbinate or from the nasal floor. Both of these sources usually provide a generous free graft (if carefully dissected), which can usually cover most of an expanded sellae and even a portion of the suprasellar space. This is also recommended in the absence of a leak, as a thinned, stretched diaphragma sellae can often leak or pull away from the anterior dura postoperatively due to unintentional valsalva maneuvers.

The "gasket seal" technique has gained some popularity due to extremely low leak rates [6]. This technique provides an extremely effective buttress, using an absorbable plate to wedge an allo- or autograft (e.g., fascia lata) into the defect. There are, however, drawbacks to this technique in that it requires creation of a narrower bony opening in order to leave adequate bone for securing the plate and there

are reports of internal carotid artery (ICA) injury from rigid bone grafts or plates during placement or due to postoperative migration.

The "button" technique has also shown promise as a nonvascularized reconstruction technique [7]. Two layers of allo- or autograft (fascia lata) are centrally sutured to each other, allowing for their edges to be placed in apposition intra- and extradurally. The suturing reduces the potential of migration of the intradural graft and may also provide some additional degree of seal.

Vascularized Reconstruction

Vascularized reconstruction revolutionized endoscopic endonasal skull base surgery (ESBS) in much the same way that vascularized pericranial flaps revolutionized open transcranial anterior skull base surgery. Prior to their introduction, unacceptable CSF leak rates ranged as high as 70% for some tumor types [8]. As a result, these flaps were the savior of "extended" or "expanded" techniques, with leak rates around 5–10% for even the most difficult parasellar defects [9, 10].

Vascularized reconstructive options following transsphenoidal surgery include the nasoseptal flap, middle turbinate flap, and the inferior turbinate/lateral nasal wall flap. Regional scalp flaps, such as the extracranial pericranial flap (EPF) and temporoparietal fascial flap (TPFF), are rarely needed or used for sellar/parasellar defects, but can be resorted to in case of local flap failure or in revision surgery when local flap pedicles have not been preserved.

The nasoseptal flap [11] is the workhorse flap for endonasal cranial base reconstruction and can be used for defects from the anterior cribriform to the clivus (Fig. 18.1). Its pedicle is based on the posterior septal branches of the sphenopalatine

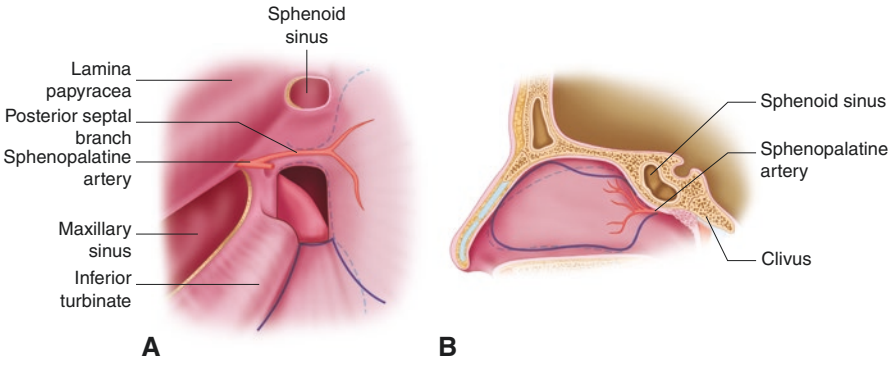

Fig. 18.1 Drawing showing the design of the nasal septal flap. (**a**) The vascularized pedicle is based on the posterior nasal branches of the sphenopalatine artery. The superior cut starts at the sphenoid ostium. The inferior cut follows the posterior choana to the junction of the nasal septum and nasal floor. (**b**) The superior cut spares the olfactory mucosa but includes the superior septum anterior to the middle turbinate. The superior and inferior incisions are connected anteriorly at the mucocutaneous junction

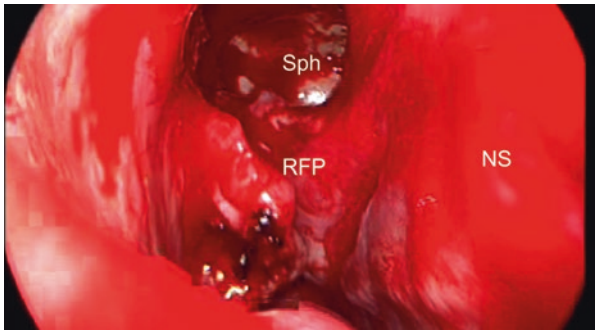

Fig. 18.2 Intraoperative, endoscopic endonasal view showing access to the sphenoid (*Sph*) with preservation of the rescue flap pedicle (*RFP*), allowing harvest of the nasal septal flap at the end of surgery if needed. *NS* nasal septum

artery. These exit the sphenopalatine foramen just deep to a small projection of the bone, the crista ethmoidalis, near the posterior attachment of the middle turbinate. There are generally two vessels that supply the flap and the vascular pedicle extends from the sphenoid os to the posterior choana.

If a significant cerebrospinal fluid leak is anticipated during surgery, it is preferable to raise the nasoseptal flap at the beginning of the operation so that the vascular pedicle is not compromised during the surgery. If a significant cerebrospinal fluid leak is not expected, the flap pedicle can be preserved on one side and a flap can be elevated at the end of the operation only if it is needed (Fig. 18.2). It is imperative to protect the vascular pedicle during the surgery from instrument trauma so that the vascularity of the flap is not compromised.

The nasoseptal flap may be harvested from either side of the septum; the laterality depends on multiple factors. If the tumor extends more to one side (e.g., cavernous sinus invasion), the flap is elevated on the contralateral side so that the flap pedicle does not hinder access to the tumor. If there is a severe septal deviation, it is preferable to raise the flap on the concave side of the septum to avoid tearing the flap. If everything is equal, an argument can be made to elevate the flap on the side opposite the endoscope. There is greater risk of trauma to the septal mucosa on the side opposite the endoscope due to repetitive blind passage of instruments. This can result in a septal perforation if the flap is harvested on the side of the endoscope.

The inferior incision is made first, starting at the top of the posterior choana, inferior to the posterior septal arteries, along the posterior edge of the septum (Fig. 18.3). The incision continues anteriorly along the junction of the nasal septum and nasal floor to the mucocutaneous junction at the nasal vestibule. The superior incision starts at the sphenoid os and runs parallel to the skull base, approximately 1 cm below the olfactory sulcus, thereby preserving olfactory function. Once the superior incision passes the anterior attachment of the middle turbinate, it can be directed more superiorly to capture all of the mucosa of the anterior-superior septum. This part of the septal flap is thicker and provides the most distal reach of the flap. A vertical incision just inside the mucocutaneous junction of the nasal vestibule now connects the superior and inferior incisions anteriorly. All of these mucosal incisions can be made either with a needle-tip monopolar electrocautery (low energy setting) with a slight bend on the tip or with a sickle blade knife.

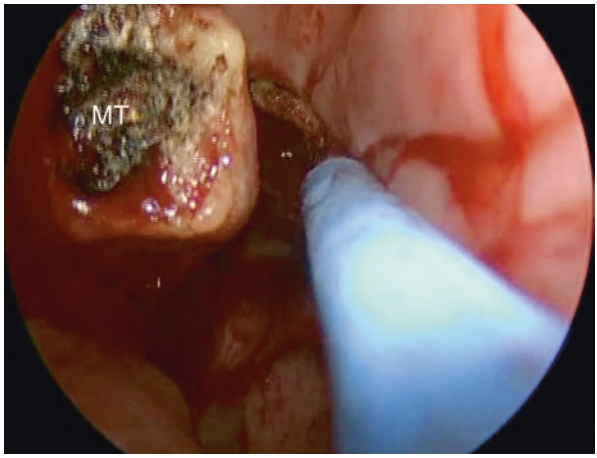

Fig. 18.3 Intraoperative, endoscopic endonasal view showing a needle-tip monopolar cautery being used to make the inferior cut for the nasal septal flap at the roof of the choana, just deep to the middle turbinate stump (*MT*)

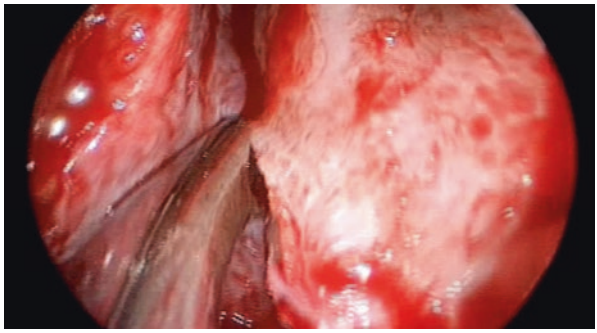

Fig. 18.4 Intraoperative, endoscopic endonasal view showing a dissector elevating the nasal septal flap by separating the mucoperichondrium and bony nasal septum

Common mistakes include not utilizing all of the septal mucosa anteriorly and superiorly. Care should be taken to avoid transgressing the underlying cartilage of the septum, which could result in a perforation. Dissection of the flap is performed between the perichondrium and cartilage/bone of the septum in an anterior to posterior direction (Fig. 18.4). If the previously described cuts are made completely, the flap will dissect easily back to its pedicle at the sphenoid rostrum and can then be displaced into the nasopharynx. Otherwise, the cuts can be completed with pistol-grip (Kurze or sinus) scissors. The flap is more difficult to dissect along the junction of the septal cartilage and palatal bone; sharp dissection may be necessary here to avoid tearing the flap.

When it is time to reconstruct the dural defect, an inlay collagen graft is placed between the brain and the dura. If the defect is small, the entire defect is then covered with the nasoseptal flap. It is important to confirm that the entire flap is in contact with the bone and dura; all remnants of mucosa and bone chips need to be removed. There should be no tension on the flap pedicle. If the dural defect is large with a high-flow leak, an onlay fascial graft may be interposed between the inlay

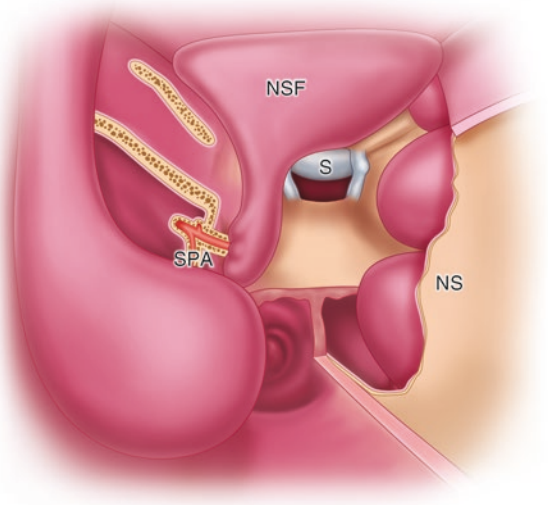

Fig. 18.5 Drawing showing placement of the vascularized nasal septal flap (*NSF*) over a suprasellar defect. *S* sella, *NS* nasal septum after mucosa flap elevated, *SPA* sphenopalatine artery

graft and the nasoseptal flap. The nasoseptal flap has significant size and mobility for reconstruction, and is ideal for the sella and parasellar regions. Coverage for suprasellar tumors, which generally result in high-flow leaks, can be provided by placing the flap pedicle against the lateral nasal wall or along the floor of the sphenoid sinus (Fig. 18.5). The reach of the flap can be augmented, if necessary, by filling the clival recess with adipose tissue, deep to the flap pedicle.

The flap is covered with layers of Surgicel, tissue glue, and Gelfoam to secure the flap edges. The reconstruction is then supported with Merocel tampons or a Foley balloon catheter inflated with saline. The exposed cartilage of the donor site on the anterior nasal septum is covered with a free mucosal graft from a resected middle turbinate or nasal floor to promote rapid mucosalization and minimize postoperative crusting. Silastic septal splints are placed bilaterally.

The nasoseptal flap can be modified to accommodate different size defects. Without prior knowledge of the exact dimensions of the dural defect, a standard flap (as outlined above) is adequate for most situations. If a larger defect is anticipated, the flap can be widened by incorporating the mucosa of the nasal floor as far as the inferior meatus. Prior septal surgery (septoplasty, transseptal approach to the sella) is not a contraindication to raising a nasoseptal flap. A plane of dissection can usually be developed between the fascial layers of the mucosa on each side without perforation of the flap. If the posterior septum cannot be dissected, the full thickness of the septum, with mucosa on both sides, can serve as the pedicle of the flap. If there is a preexisting septal perforation, the flap can be designed above or below the perforation, or the perforation can be included in the flap with the addition of a fascial graft between the dura and the flap at the site of the perforation.

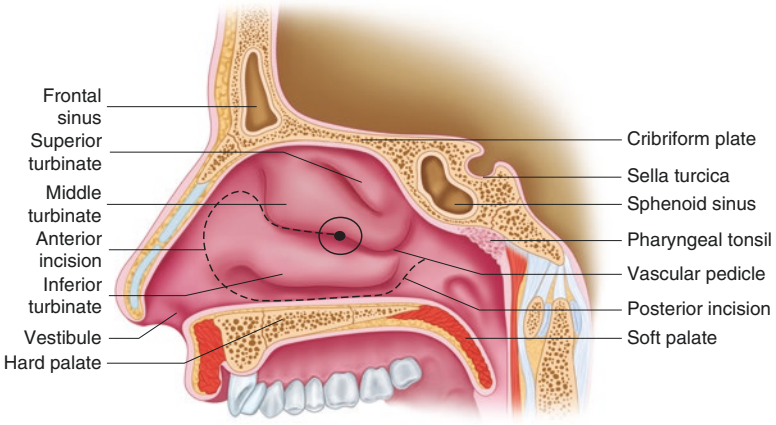

Fig. 18.6 Illustration of a right-sided inferior turbinate flap. The superior incision extends from the maxillary antrostomy to the anterolateral nasal wall. The inferior incision extends from the top of the Eustachian tube to the nasal floor. The flap is pedicled on the lateral nasal branch of the sphenopalatine artery

Other Vascularized Flaps Following Pituitary/Parasellar Surgery

Middle Turbinate Flap

A vascularized flap can also be harvested from the middle turbinate and rotated to cover a sellar or suprasellar defect [12]. This flap, however, is technically more challenging than the nasoseptal flap, requiring careful dissection of the thin bone of the turbinate process. The size of the flap is variable and has a limited arc of rotation and reach. The mucosa is not as thick as a free mucosal graft. These flaps are suitable for only small sellar or suprasellar defects.

Inferior Turbinate/Lateral Nasal Wall Flap

The lateral nasal wall flap is based on the axial blood supply to the inferior turbinate (branch of the sphenopalatine artery) and is a reliable alternative when other local options have failed (Fig. 18.6) [13–15]. The standard flap consists of the mucosa lining the inferior concha, nasal floor, and the superolateral nasal wall (Fig. 18.7). This flap is very difficult to dissect from the inferior concha and tends to retain its curved shape in this region. It has a limited arc of rotation and limited reach. It is best suited for small- or medium-sized defects of the middle clivus and sellar regions (Fig. 18.8).

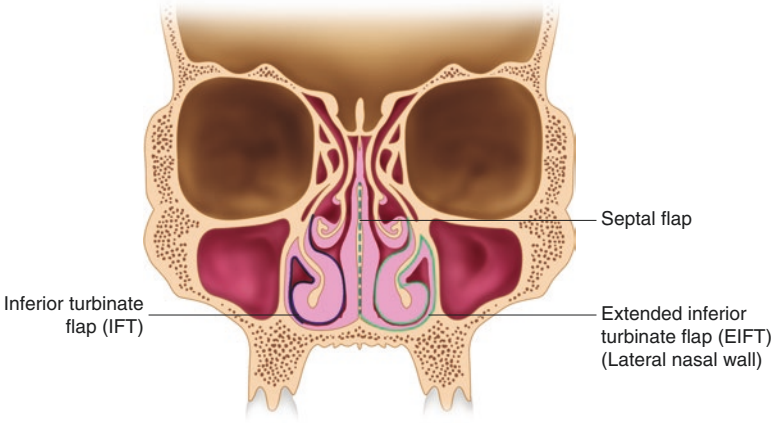

Fig. 18.7 The standard inferior turbinate flap includes the mucosa of the inferior turbinate and inferior meatus. The flap may be extended to include the mucosa of the nasal floor and nasal septum

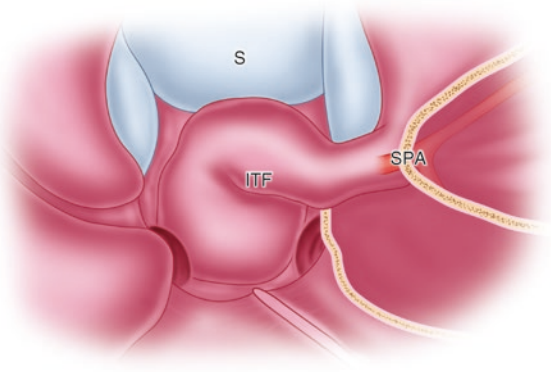

Fig. 18.8 Drawing showing a left-sided, vascularized inferior turbinate flap (*ITF*), with its blood supply from the sphenopalatine artery (*SPA*), covering a clival defect. S sella

The inferior turbinate flap can be extended to include the mucosa of the nasal septum (Fig. 18.7) [14]. An extended inferior turbinate flap has a large surface area that allows coverage of large defects (Fig. 18.9). The septal portion of the flap probably has a random blood supply, however, and may not be as reliable as a nasoseptal flap. This flap is an option when a nasoseptal flap is not available due to prior surgery with sacrifice of the posterior septal arteries or tumor involvement of the anterior face of the sphenoid sinus.

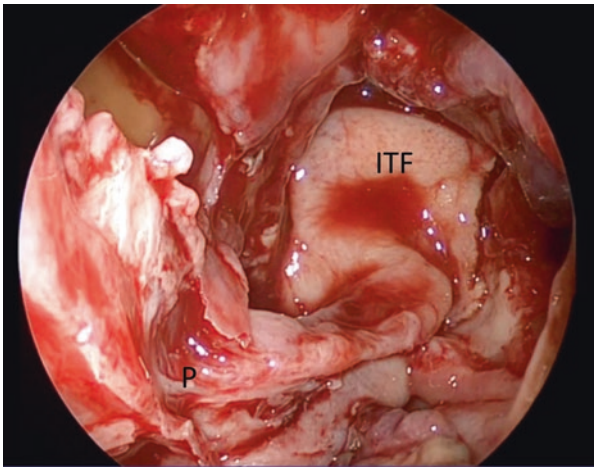

Fig. 18.9 Intraoperative, endoscopic endonasal view showing final placement of an extended right inferior turbinate flap (*ITF*) over a sellar defect. *P* pedicle of flap at the sphenopalatine foramen

Postoperative Care

Lumbar drainage is not routinely employed for sellar and suprasellar defects. A randomized trial of lumbar drains did not demonstrate statistically significant benefit in such situations (Zwagerman, Gardner, et al; 2017), but this could be related to the extremely low risk of leak with vascularized reconstruction in these situations.

Nasal packing is removed after 5–7 days, depending on the size of the dural defect and the characteristics of the patient. Patients are advised to refrain from activities that increase cerebrospinal fluid pressure for a few weeks. The septal splints are removed at 1 week if a nasoseptal flap was not used and at 3 weeks if a nasoseptal flap was used. This helps to protect the healing septum and promote mucosalization. Gentle debridement of the surgical site is performed as necessary and the patient is closely monitored for evidence of a cerebrospinal fluid leak.

Postoperative imaging should be studied to evaluate for the enhancement of vascularized flaps, which is similar to the normal surrounding mucosa (Fig. 18.10). Absence of enhancement should lead to suspicion of a devascularized flap and close observation for associated risk of flap necrosis (see below).

Complications

Postoperative cerebrospinal fluid leaks are impacted by multiple factors, but most often it is a consequence of improper technique with poor apposition of the flap. Patient characteristics or activities that impair wound healing or increase CSF pressure may also contribute to a postoperative CSF leak (Fig. 18.11). Postoperative CSF leaks are managed emergently with return to the operating theater within 24 h for endoscopic repair. In most cases, there is a small leak at the edge of the flap that can be repaired with repositioning of the flap or augmentation with fascia and fat.

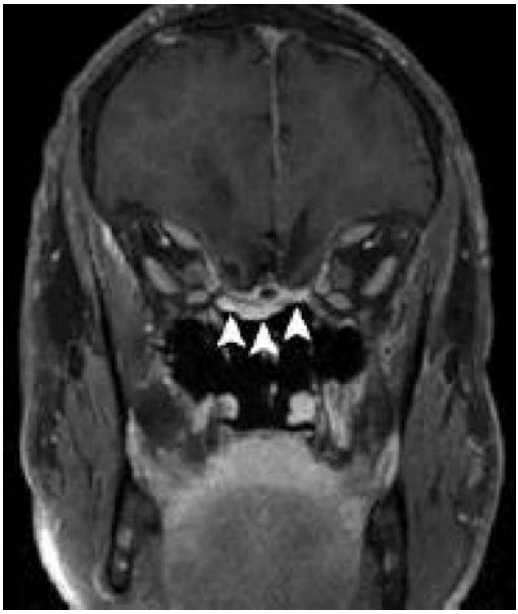

Fig. 18.10 Postoperative MRI demonstrates enhancement (*arrow heads*) of a vascularized nasoseptal flap

Flap necrosis is a rare event and results from loss of the blood supply. This is more likely to occur in revision cases where the flap pedicle is already narrowed. The flap pedicle should be protected from trauma (sharp instruments, powered instruments, and electrocautery) during the operation. An early postoperative scan will demonstrate the enhancement of a vascularized flap. If the flap does not enhance and/or the patient develops meningitis, flap necrosis should be suspected. If present, the nonviable tissue is debrided and the reconstruction is revised [16].

Donor site morbidity of a nasoseptal flap includes nasal crusting and possible septal perforation. Mucosalization of the septum is complete within several months and can be minimized with mucosal grafting of the donor site. A septal perforation can be prevented by avoiding intraoperative trauma to the septal mucosa opposite the flap. A decrease in olfactory function can also be observed. This may result from placing the superior septal incision too close to the olfactory mucosa.

Conclusions

A tiered approach to reconstruction of dural defects following transsphenoidal skull base surgery is employed. Nonvascular, multilayer fascia and free mucosal grafts are effective for small low-flow leaks. The vascularized nasoseptal flap is the standard for larger defects and is suitable for reconstruction of sellar, suprasellar, and clival defects. Proper design of the flap with preservation of the vascular pedicle ensures a high degree of success.

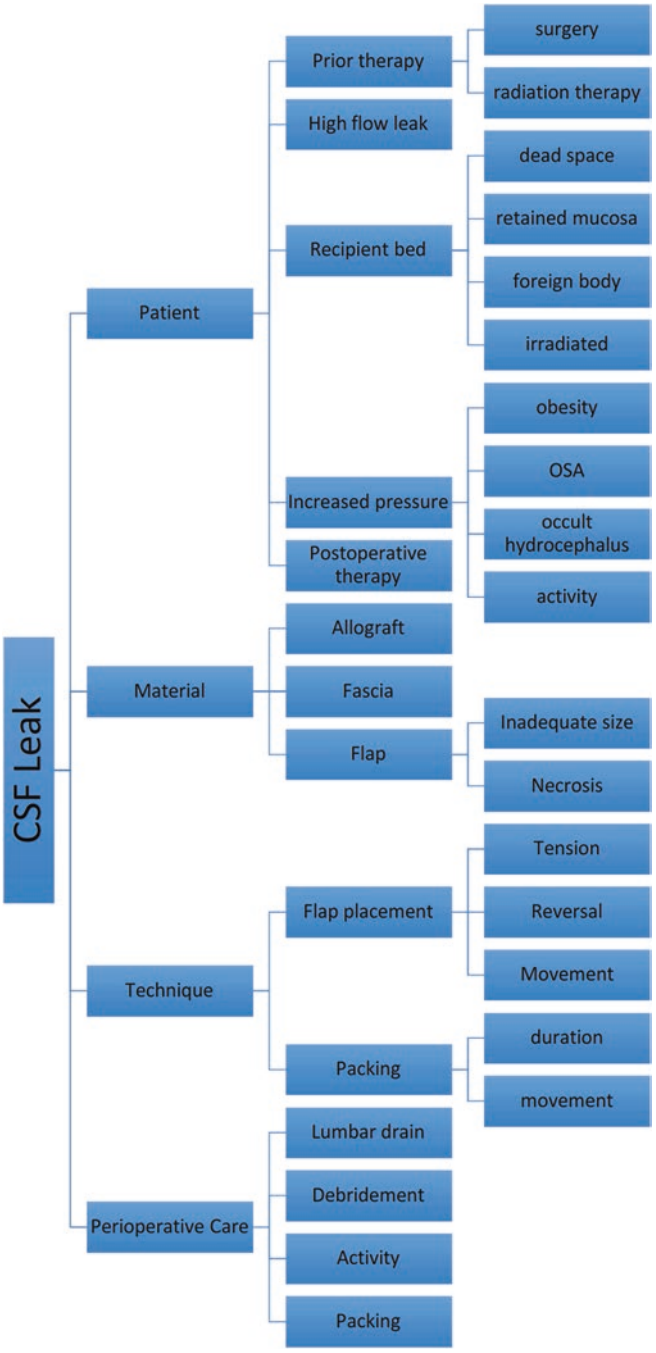

Fig. 18.11 Root cause analysis for postoperative cerebrospinal fluid (*CSF*) leak

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Complications with Transsphenoidal Surgery: A Review

19

Complications of Transsphenoidal Surgery

Garni Barkhoudarian and Daniel F. Kelly

Introduction

Complications are a known fact with any surgery. These can occur at any type of institution (academic or private) and even in the most experienced of hands. There always remains a balance between the indications of surgery, intended extent of tumor resection, and risk of a major complication. Technological advances in neurosurgery have shaped the course and success of transsphenoidal surgery. Though Harvey Cushing had championed the transsphenoidal approach for pituitary tumors in his first few decades of practice, the abandonment of this approach in the latter part of his career reflected the immature technology to allow for safe and successful surgery.

The transsphenoidal approach was utilized by only a handful of surgeons after Dr. Cushing's retirement. Only with the advent of the surgical microscope (borrowed from the otologists) and video fluoroscopy did interest resume for this approach. Other advances, such as long, bayonetted, and pistol-grip instruments, neuronavigation, Doppler ultrasound, and high-definition endoscopy, have progressively improved transsphenoidal tumor resection capacity while decreasing the incidence of major complications. This review discusses the common major and minor complications that have been reported with transsphenoidal surgery, with a focus on complication prevention in each phase of patient care – from the clinic through the operating suite to recovery at home.

G. Barkhoudarian, MD (✉) • D.F. Kelly, MD
Pacific Pituitary Disorders Center, John Wayne Cancer Institute
at Providence Saint John's Health Center, Santa Monica, CA, USA
e-mail: barkhoudariang@jwci.org

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_19

Phases of Care

Surgical complications can be organized by numerous methods. One logical approach is by segmenting these along the phases of patient care (Table 19.1). Pituitary tumor patients can find themselves in the surgeon's office from a variety of avenues (endocrinologist, ophthalmologist, neurologist, urologist, reproductive specialist, the internet, etc.). This starting point leads to the preoperative and preincision phases. Surgery itself can be divided into approach, tumor resection, and skull base closure phases. This is followed by the immediate postoperative phase (inpatient and outpatient) and, finally, the long-term management phase.

The Clinic: Patient Selection

Complication prevention begins in the clinic, before surgery is ever discussed. Though there are many clear-cut indications for surgery (pituitary apoplexy, macroadenoma with bitemporal hemianopsia, acromegaly, etc.), often the most difficult decision for the surgeon is whether and when to operate. This certainly applies to patients with truly incidental pituitary adenomas and Rathke cleft cysts (RCCs), tumors with equivocal hyperprolactinemia, unclear diagnoses of Cushing disease, and lesions that mimic tumors.

Certainly, it is well accepted that the first lines of therapy for prolactin-secreting adenomas are dopamine agonists. However, physicians should critically evaluate patients with mildly elevated prolactin levels and microadenomas, particularly in patients with minimal symptoms. Other causes of hyperprolactinemia should be considered, as seen with antipsychotic and neuroleptic antiemetic medications. Macroprolactinemia (big-prolactin) – a variant present in X patients obscuring prolactin levels – should also be considered.

Preoperative imaging should be carefully reviewed. High-resolution "pituitary protocol" MRIs should always be obtained given the improved visualization of the sellar contents. Non-neoplastic entities should be considered, especially when the imaging does not demonstrate an obvious distinction between lesion and normal gland. These include patients with lymphocytic hypophysitis, severe primary hypothyroidism, and intracranial hypotension (Figs. 19.1, 19.2, and 19.3). Other caveats include differentiating sellar arachnoid cysts from primary empty sella (Fig. 19.4). Cisternography may be helpful to determine empty sella, and one should evaluate

Table 19.1 Phases of care influencing pituitary patient surgical outcomes

Phases of care
Patient selection
Preincision
Surgical approach
Tumor resection
Closure
Inpatient postoperative management
Outpatient postoperative management

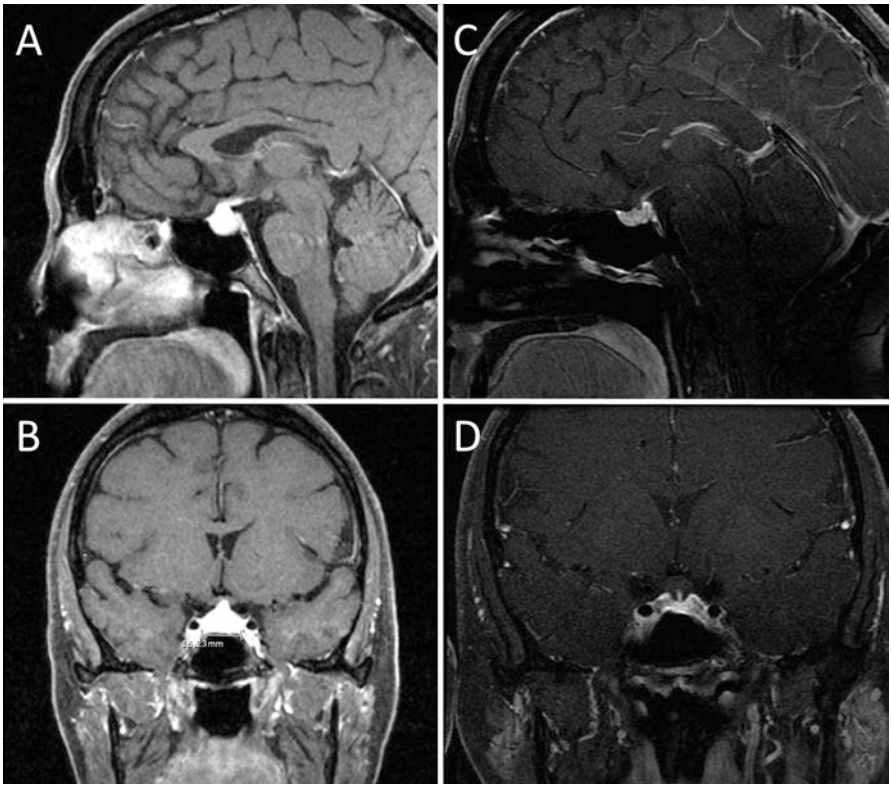

Fig. 19.1 A 54-year-old female with headaches and a brightly and homogenously enhancing, symmetric pituitary gland (**a**, **b**). She was treated with prednisone with resolution of headaches and pituitary enhancement/enlargement (**c**,**d**)

patients for signs or causes of elevated intracranial pressure (Chiari I malformation, transverse sinus thrombosis, pseudotumor cerebri, etc.).

The surgeon should also be aware of their capabilities as well as those of their institution. One should consider their surgical experience with regards to complex lesions requiring extended endonasal approaches and be intimately familiar with the specific surgical anatomy as well as closure techniques to prevent CSF (cerebrospinal fluid) rhinorrhea. A surgical staff unfamiliar with these operations can affect intraoperative processes and surgical outcomes. Similarly, postoperative care relies on nurses well trained in the early recognition of postoperative complications to prevent catastrophes such as untreated diabetes insipidus (DI) or acute postoperative vision loss.

Not all parasellar tumors should be treated via an endonasal approach. The choice of the most appropriate surgical approach should be carefully determined prior to entering the operating suite. In particular, this applies to certain tuberculum sella meningiomas, craniopharyngiomas, chordomas, and arachnoid cysts (Figs. 19.5 and 19.6) [1]. In some cases, a craniotomy may be preferable to an extended endonasal approach.

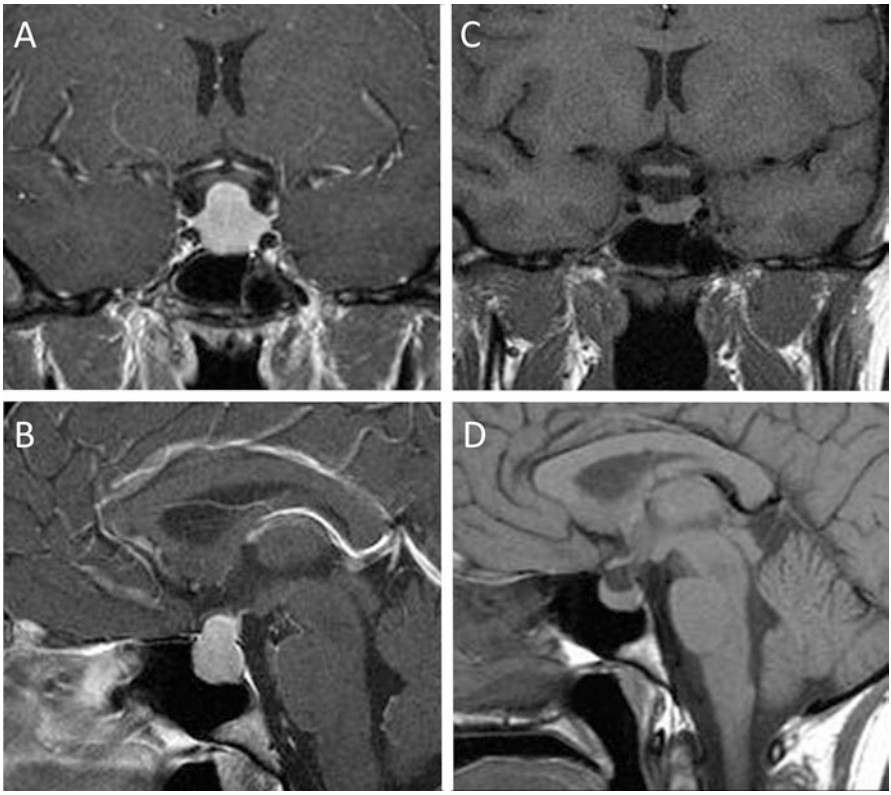

Fig. 19.2 A 23-year-old female with headaches and a homogenously enhancing, symmetric pituitary gland (**a**, **b**) was found to have profound primary hypothyroidism with free T4 < 0.4 ng/dL and TSH 1576 IU/mL. The pituitary enlargement resolved with levothyroxine therapy alone (**c**, **d**)

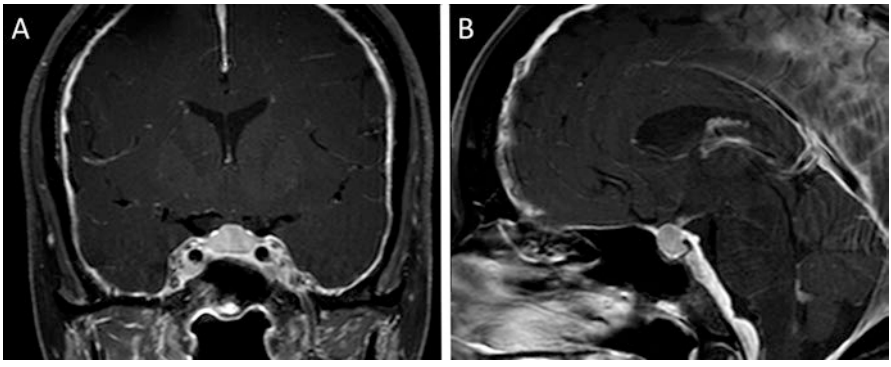

Fig. 19.3 A 55-year-old female with a history of hydrocephalus treated with VP shunting 23 years prior to imaging. There is profound pachymeningeal enhancement of the dura reflective of chronic intracranial hypotension (**a**, **b**). The pituitary gland is enlarged as a result of intracranial hypotension as well. The patient had normal pituitary function

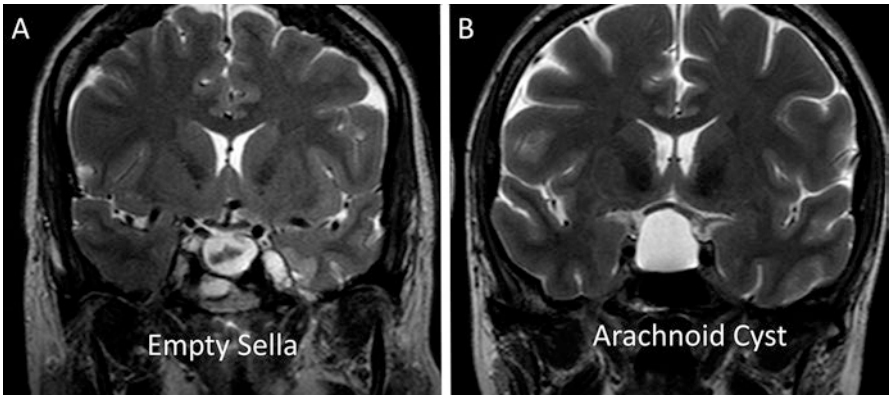

Fig. 19.4 Empty sella (**a**) and sellar arachnoid cyst (**b**). Note the CSF flow artifacts with the empty sella (**a**) as well as the evidence of increased pressure and upward deviation of the optic apparatus with the arachnoid cyst (**b**)

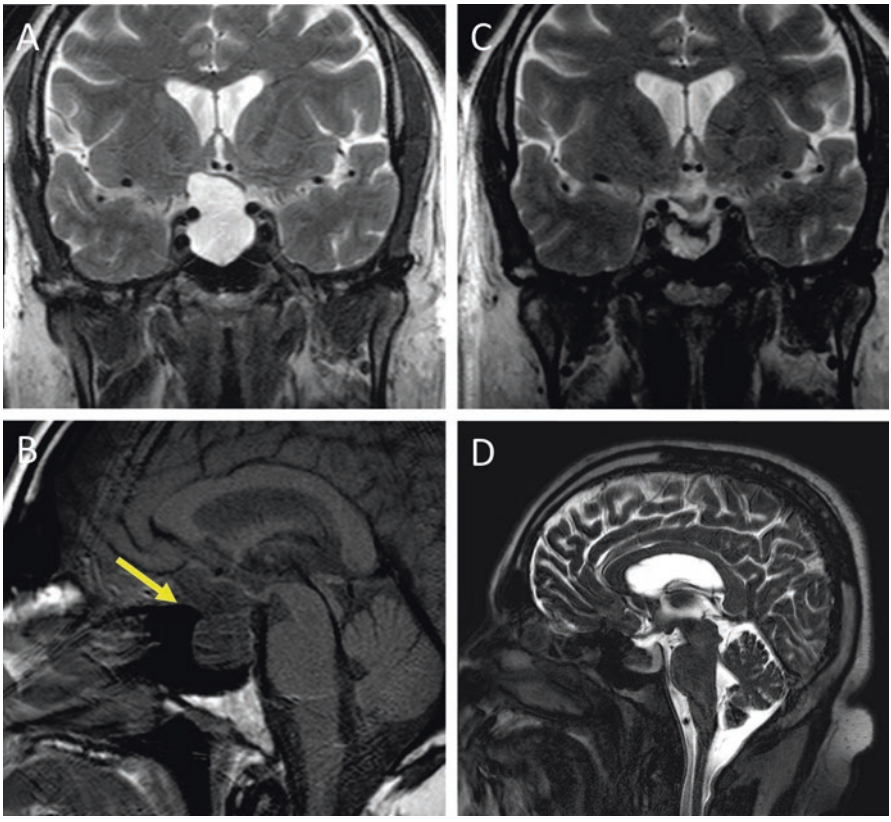

Fig. 19.5 MRI (**a**, **b**) demonstrating a growing sellar/suprasellar arachnoid cyst with significant anterior planum sphenoidale extension (*arrow*). Given this anterior extension, this was approached via a supraorbital "eyebrow" craniotomy with fat graft placement into the cyst cavity. This patient has not had cyst recurrence at 1-year follow-up (**c**, **d**)

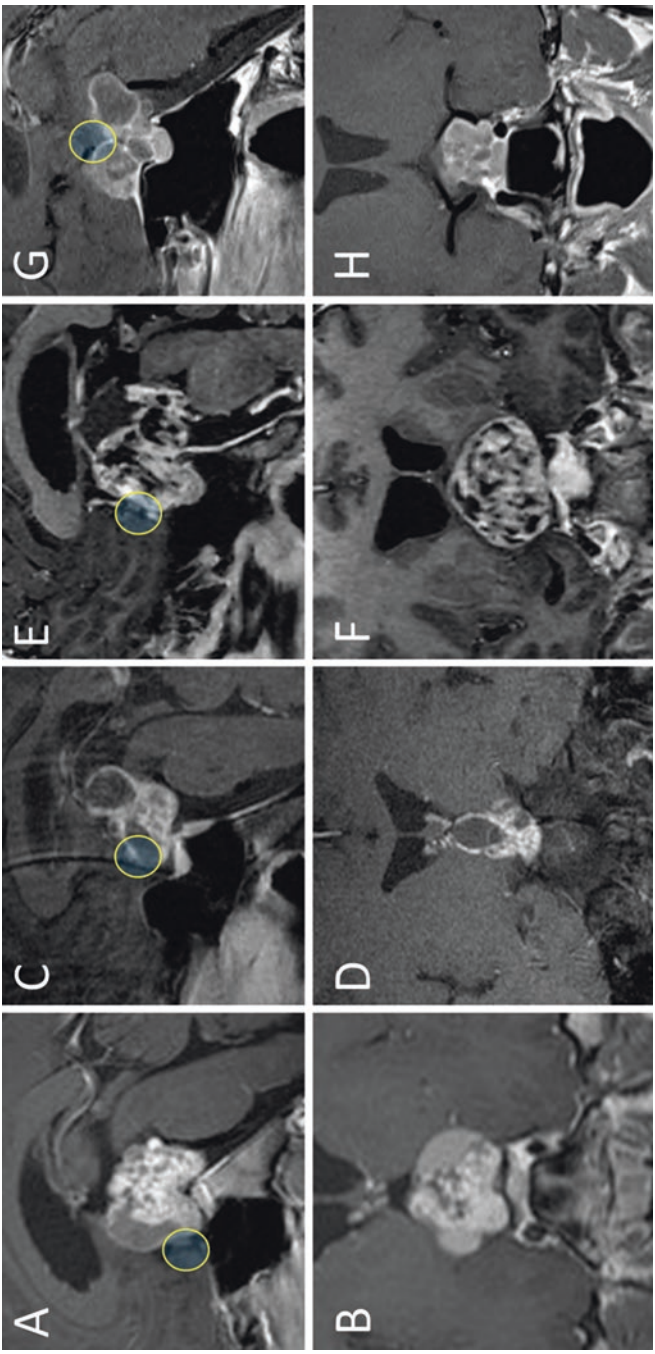

Fig. 19.6 Examples of craniopharyngioma that are ideal for endonasal transsphenoidal surgical resection (**a**–**f**). Note the location of the optic chiasm (*oval*) with the tumor retrochiasmal. The tumor in figure (**g**/**h**) is subchiasmal with lateral extension, potentially more ideal for a transcranial approach

Operating Suite – Preincision

Once the decision of surgery is made, the preincisional phase has numerous decisions that can affect outcomes. Many of these are already incorporated into the surgeon's routine, but some certainly should be assessed in each case. Rarely are major complications due to preincisional actions. However, routine insertion of arterial lines or central venous catheters can cause the occasional pneumothorax or septicemia. Indications for other invasive devices, particularly lumbar drains, should be carefully considered and will be discussed further.

Surgical adjuncts, such as neuronavigation, have positively impacted the safety of transsphenoidal surgery, both for the patient and for the surgeon. Video fluoroscopy, the traditional "navigation" device, had been used for transsphenoidal surgery since the 1960s [2]. This cumbersome technology affected positioning and operating room ergonomics and exposed OR staff to radiation. At our institution, we advocate the routine use of stereotactic neuronavigation, in part to be used as a teaching tool. It is most helpful in reoperations, where the normal anatomy is distorted, potentially preventing inadvertent injury to the surrounding neurovascular structures. These devices never replace the reliance on anatomical knowledge and preoperative imaging analysis, though.

Ultimately, every intervention performed on the patient has a potential for negative consequences and its risk/benefit ratio should be carefully assessed. The majority of these in the preincision stage are associated with "minor" complications, but can certainly affect the outcome of surgery, even if just causing increased discomfort to the patient. These will be further discussed in the section "Minor Complications."

Failure to provide therapy can also affect outcomes in this phase. Timely and appropriate corticosteroid replacement – at stress dose levels – is necessary to prevent Addisonian crisis during or after surgery. Recognition of diabetes insipidus is necessary to prevent major fluid shifts and concomitant sodium flux during surgery. In these situations, collaboration with an endocrinologist can be helpful for optimal patient management.

Surgical Approach

The pituitary surgeon, focused on reaching the sella, recognizes the major structures to protect during the approach. In the nasal cavity, the primary focus is to protect the sphenopalatine artery and to avoid breach of the frontal fossa. In the sphenoid, the focus shifts to the carotid arteries and optic nerves. Tools such as neuronavigation and micro-Doppler probes help protect these structures.

However, in this "fly-by" approach to the sella, other less critical, but still important structures can be taken for granted. Preservation of the olfactory nerves and cartilaginous nasal septum prevent anosmia and nasal crusting. Attempts to preserve the turbinates can help maintain laminar air flow long after the nasal cavity has healed. Preservation of the sphenoid sinus mucosa, when possible, can maintain mucociliary function, decreasing the incidence of postnasal drip. Finding and

preserving the Vidian nerve can decrease the possibility of xerophthalmia from lacrimal gland dysfunction [3]. Addressing these minor issues, stressed by the otorhinolaryngologists, can help improve the postoperative quality of life.

Tumor Resection

Once in the sella, the primary goals become maximal safe resection of the tumor and gland preservation. In the setting of a soft pituitary adenoma, the tumor essentially delivers itself. However, for more fibrotic, hemorrhagic, or invasive tumors, there is increased concern of pituitary gland damage as well as injury to the surrounding vasculature. Cavernous sinus invasion can jeopardize the carotid artery as well as the abducens nerve. Even with an intact cavernous sinus dura, careful manipulation of the carotid artery is important in the vasculopath patient to prevent embolic stroke.

Pituitary dysfunction is often seen with macroadenomas, with or without hemorrhagic transformation. Numerous studies have assessed the probability of pituitary gland recovery of function. There is also an inherent risk of new pituitary dysfunction. It is debatable whether pituitary dysfunction is a major complication or a potentially avoidable surgical risk. However, quality of life studies consistently demonstrate a negative correlation with hypopituitarism [4, 5]. Any patient reliant on desmopressin can speak to the difficulties of maintaining fluid and sodium balance long term – particularly those who have had hypothalamic dysfunction after craniopharyngioma resection [6]. These issues will be discussed further in the spectrum between "minor" and "major" complications.

Closure

The recognition and repair of intraoperative cerebrospinal fluid leaks are routine for the experienced pituitary surgeon. A CSF leak grading system is a helpful guide for surgical repair, but other factors should be considered [7]. These include the regional anatomy of the sella and sphenoid that the surgical team should take into account in deciding the repair method. Such details include the presence of a nook capable of holding a fat graft; whether the carotids are exposed or whether it is safe to insert a rigid buttress, and the availability of vascular pedicled flaps, the body habitus, and comorbidities of the patient (obesity, sleep apnea, emphysema, etc.) that can increase the risk of postoperative Valsalva events. These can "upgrade" or "downgrade" routine maneuvers for a particular type or location of a leak. The incidence and prevention of such leaks will be discussed below, as well as the utility of CSF diversion.

Postoperative Management: Inpatient

The postoperative patient care is critical to maintain good surgical outcomes. Well-trained nurses, whether in an intensive care unit or specialized floor, can help recognize early postoperative vision changes or fluid shifts, allowing timely urgent

management. Disease-specific issues include the scheduled assessment of cortisol levels in patients with Cushing disease and rapid replacement once symptomatic or "crashed." There has been a trend to discharge pituitary patients relatively early. Hence, some of these issues are managed as an outpatient with good patient education. Paramount to this is the assessment of postoperative delayed hyponatremia, often called SIADH (syndrome of inappropriate antidiuretic hormone), at 5–7 days following surgery, accomplished with routine outpatient serum sodium level laboratory assessments [8].

Postoperative Management: Outpatient

As the patient continues to heal from the immediate effects of surgery, there is a role for sinonasal disease management (including periodic debridements of the nasal cavity to prevent adhesions or sinusitis). At our institution, patients are seen by the ENT surgeon at least 2–3 times with endoscopic evaluation and debridements at each visit. Delayed postoperative imaging can help detect the onset of new sinusitis that should be addressed.

Major Complications

Vascular Injury

Vascular injury can be divided into four aspects with regard to transsphenoidal surgery, each with its spectrum of severity. These include sphenopalatine artery hemorrhage with arterial epistaxis, tumor cavity hemorrhage, carotid artery injury or stroke, and Circle of Willis arterial branch injury (e.g. superior hypophyseal artery injury).

During transsphenoidal exposure, the sphenopalatine arteries are identified and attempted to be preserved. When severed, these arteries are cauterized, usually at the level of their exiting foramen (the palatovaginal canal). In these cases, delayed arterial epistaxis can occur as the eschar matures during the healing process [9–12]. The incidence of delayed arterial epistaxis has been reported in up to 7% of cases in large series [13–19]. Severe arterial epistaxis can have dire consequences including hypovolemic shock as well as asphyxiation, if not treated quickly. To prevent this complication, some surgeons have incorporated the "rescue flap" approach, where no nasal cavity mucosa is resected, but rather incised sharply (Fig. 19.7) [20]. This preserves the sphenopalatine artery and not only prevents epistaxis, but also allows for future elevation of pedicles nasoseptal flaps which can be utilized during the original exposure or at time of reoperation. Griffiths et al. recently published their series of 161 patients, in which 80% underwent elevation of bilateral rescue flaps. None of these patients experienced arterial epistaxis and three ultimately were converted to pedicled nasoseptal flaps.

Tumor cavity hemorrhage can occur in approximately 0.7–2.9% of patients, primarily in those harboring pituitary macroadenomas [9, 14, 21]. Intraoperative bleeding in the sella is often venous and can be effectively controlled with

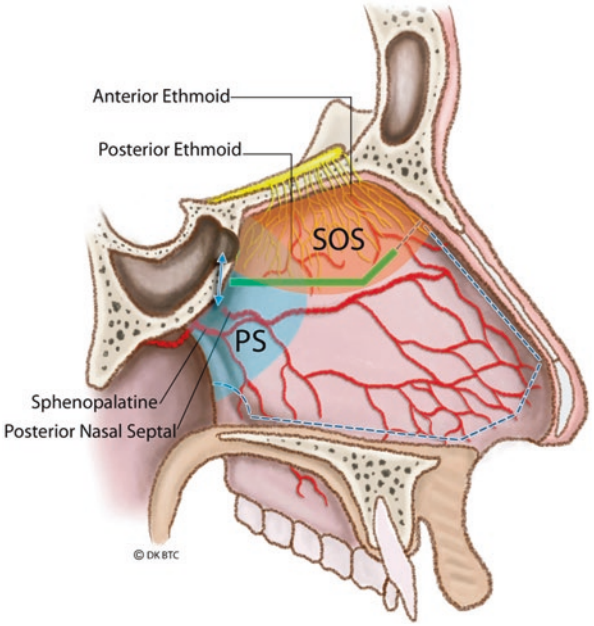

Fig. 19.7 Figure of incision for "rescue flap" (*green line*) allowing for preservation of the nasal septal branch of the sphenopalatine artery as well as the olfactory fibers. Note that this exposure preserves the ability to perform a pedicled nasoseptal flap during the operation or in the future

irrigation, thrombin-soaked collagen sponge, hydrogen peroxide, or even elevating the head of the bed. On occasion, capsular arteries can bleed persistently and, if not cauterized at the time of surgery, can result in postoperative hemorrhage. Most tumor bed hemorrhages can be observed and will absorb over time. However, if there is new onset vision loss or pituitary dysfunction, then early surgical evacuation is indicated to prevent irreversible deficits.

Carotid artery injury is a dreaded complication in transsphenoidal surgery, occurring in 0–3.8% of large series [14, 21–25]. Many experienced pituitary surgeons have experienced such an injury in their career. The most important aspect of this potential complication is its prevention. This begins with careful preoperative analysis of the course of the carotid arteries and their branches with respect to the tumor. In complex cases or reoperations, CT angiography may be helpful to gain a better understanding of this anatomy as well as the health of the carotid arteries. Neuronavigation is a useful adjunct, particularly when utilizing the MIP vascular imaging as the navigation source. One should recognize that sphenoid sinus septations are rarely midline markers and often (70–80%) lead to one or both of the carotid arteries [26]. In cadaver studies, bony dehiscence over the carotid artery has been noted up to 16% of cadaver specimen [27]. Hence, sharp dissection of the mucosa overlying the carotid artery should be avoided.

To date, however, no technology has better safety advantage over the micro-Doppler. This device offers real-time localization of the carotid arteries and other relevant vasculature. It can be further helpful if there is inaccurate registration of the neuronavigation. It also helps the surgeon adjust to intraoperative shifts of the tumor and vasculature, particularly when used multiple times throughout the operation. In a study by Dusick et al., the introduction of the micro-Doppler in their practice decreased the carotid artery injury rate from 1.8% to 0.19% [28]. The incidence of injury for pituitary adenomas is even more rare.

Nevertheless, carotid artery injury has occurred by many types of instrument (blades, rongeurs, dissectors, drills, microdebriders, cautery, etc.). Sustaining a vascular injury is not always a life-threatening event. Hence, methodical and controlled hemostasis should be performed, much like bleeding encountered in craniotomies. The surgeon should aim to tamponade the vessel to stem the blood loss, while the nursing and anesthesia teams prepare to transfuse blood and maintain mean arterial pressure. The interventional team should be simultaneously mobilized. Once temporary hemostasis is achieved, the extent of injury should be addressed. Often, this is a small vascular injury which can be repaired with tissue or product overlays such as cotton gauze (muslin) or muscle graft (e.g. from abdominal oblique muscles at fat graft site). For larger vessel wall injury, the vessel may need to be packed off completely.

If the bleeding is under control and the patient remains stable, then further safe tumor resection may still be required, particularly for hormone-active adenomas where a cure is necessary. Often these patients are prescribed antiplatelet agents, prohibiting further surgery months or years down the line. Once the operation is determined complete and the IR team is ready, careful packing of the closure material is critical to prevent early rupture into the nasopharynx. Typical devices include urinary (Foley) catheter balloons or removable tampons. Early (same day) and frequent angiograms are necessary to identify and treat pseudoaneurysm development.

Though a catastrophic event, the mortality of carotid artery injury during transsphenoidal surgery has been noted as low as 9% in one unpublished series of 58 patients. This same series identified 10% of patients with major neurological deficits and 12% with minor deficits. This relatively low complication rate is due to patent Circle of Willis blood supply, intraoperative closure, and endovascular techniques. The ability to practice the intraoperative maneuvers after carotid injury has been simulated in various synthetic and cadaver models, allowing residents and experienced surgeons alike to advance their endoscopic hemorrhage management skills [29].

Injury or sacrifice of the branches of the carotid artery can also have detrimental outcomes. Often it is difficult to identify vascular branches off the cavernous carotid feeding the sellar tumor, but when identified, these should be divided sharply to prevent avulsion and a larger carotid tear. For suprasellar tumors, particularly craniopharyngiomas, we advocate preserving all branches of the superior hypophyseal artery. This artery supplies both the pituitary infundibulum and the optic nerve/chiasm (Fig. 19.8). Even in the setting of panhypopituitarism, it is helpful to preserve the infundibular branch of this artery as that additional tethering point prevents inadvertent injury to the optic branches.

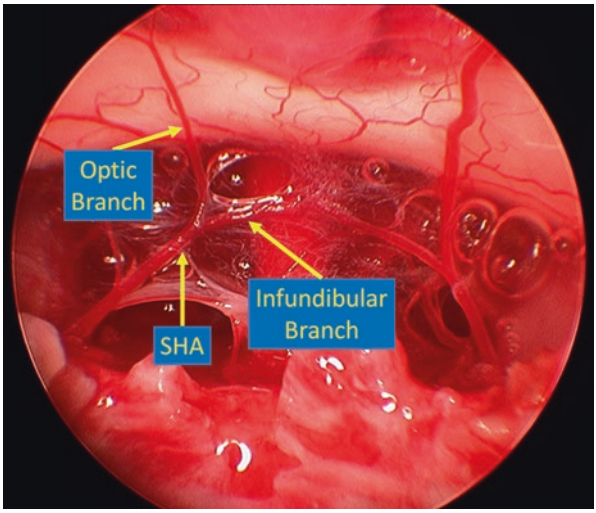

Fig. 19.8 Optic chiasm and pituitary infundibulum with superior hypophyseal artery (*SHA*) seen after tumor resection. Note the distinct branches to the optic nerve and infundibulum

Cranial Nerve Injury

The overall incidence of new cranial neuropathy including vision loss following transsphenoidal surgery is quite low, with many series reporting no permanent extra-ocular muscle weakness and minimal new vision loss [14, 21, 30]. This is primarily due to the well-contained nature of the majority of pituitary adenomas from the surrounding nerves. Subdiaphragmatic lesions rarely are associated with new postoperative vision loss, unless associated with postoperative tumor bed hematomas.

Occasionally, anatomic variations can increase the risk of optic nerve injury during sphenoid sinus dissection. This is particularly relevant to variations in sphenoid sinus pneumatization [31]. Onodi cells occur at a rate of 8–14% (based on cadaveric and imaging studies) and are variant pneumatized anterior clinoid processes [27]. This can increase risk of optic nerve injury if not recognized during sphenoid sinus surgery and the surgeon assumes that any pneumatized bone is anterior to the neurovascular structures.

Extended endonasal approaches do have a higher rate of cranial neuropathy, particularly abducens palsy following surgery for chordoma and Meckel's cave lesions [24, 32]. Lesions with extensive cavernous sinus invasion are also associated with higher abducens and oculomotor paresis. Methods to decrease these deficits include intraoperative neuromonitoring with cranial nerve stimulation for CN III and VI. Particularly with chordomas, the abducens nerve can have variable penetration of the dura with a segment traversing the interdural region. Additionally, these tumors can engulf the abducens nerve, requiring careful dissection at the level of the ponto-medullary junction.

Dissection of intracavernous lesions should involve frequent stimulation for the abducens nerve, particularly with fibrotic or adherent tumors. As one dissects further

posterior in the cavernous sinus, the oculomotor nerve comes to closer proximity with the abducens nerve and additional care should be used when manipulating tumor in this region. The abducens nerve defines the floor of the cavernous sinus and, as such, the roof of Meckel's cave. Hence, careful mapping of the course of the abducens nerve is helpful to prevent postoperative deficits when exposing and resecting Meckel's cave tumors [33].

Cerebrospinal Fluid Leakage

Repair

Postoperative cerebrospinal fluid rhinorrhea is a well described and inescapable complication with transsphenoidal surgery, particularly with extended approaches. Published rates of CSF leaks range from 2.3% to 6.0% (though select series have shown as low as 0% to greater than 10% leak rates) [7, 14, 22, 30, 34, 35]. Esposito et al. developed a helpful grading system of intraoperative CSF leaks to aid in the reconstruction and management of these dural defects. Interestingly, in their patients without identifiable intraoperative leaks, there was still a low rate of postoperative CSF rhinorrhea (0.7%) [7].

The most challenging repairs involve extended endonasal skull base approaches. Older studies reported significant postoperative leaks upwards above 20%. However, since the advent of the pedicle nasoseptal flap by Hadad and Bassagaisteguy, these rates have diminished to less than 5%, with some large series reporting no postoperative CSF leaks [36–40].

The ideal approach to managing CSF leaks is prevention and a meticulous and thoughtful repair strategy. Again, this begins with patient selection and surgical approach. However, certain risk factors should be identified to adjust one's dural repair. These include large body habitus and high BMI, sleep apnea or COPD (especially with the use of a C-PAP device), thin or absent sellar bone preventing secure rigid buttress, history of postoperative nausea and vomiting (PONV), prior surgery or radiation and sphenoid sinus morphology [41, 42]. In these patients, one should be extra vigilant in the closure, typically adding an extra measure (such as nasal packing) to prevent postoperative leaks.

The use of intraoperative and postoperative lumbar drains varies tremendously between institutions, with some surgeons utilizing these for all patients and some for none [7, 43–46]. Since the introduction of nasoseptal flaps and other pedicled flaps, the durability of dural repair has improved tremendously, decreasing the need for these invasive catheters. In our unpublished experience, we have not placed a lumbar drain in our last 280 transsphenoidal operations with no difference in our overall CSF leak rate.

Counteracting the benefits of CSF diversion are its complications – both major and minor. Overdrainage of CSF regardless of technique can result in subdural hematomas, tension pneumocephalus, and, in extreme cases, central herniation [47, 48]. If overdrainage is encountered, the patient should be placed in the

Trendelenberg position, and if herniation exists, fluid should cautiously be injected via the lumbar catheter or needle. Tension pneumocephalus can be treated with 100% oxygen in mild cases or by ventricular catheter drainage for severe symptoms [49, 50]. Additionally, lengthy CSF diversion can result in meningitis either from seeding of the catheter itself or from the intracranial aspiration of bacteria from the sphenoid sinus [51]. Prophylactic antibiotics are sometimes recommended for the duration of CSF drainage. Serial analysis of the CSF fluid is performed at various institutions, although the benefit is unclear [52].

A minor complication with lumbar intrathecal catheters is nerve root trauma with associated radiculopathy or paresthesias [53]. These symptoms are typically temporary and resolve after catheter removal. More concerning is the broken or retained catheter at the time of removal. This can be associated with nerve root irritation and can require open laminectomy for removal [54, 55].

Given these rare, but potentially life-threatening complications, judicious use of CSF drainage or access is required. Prophylactic CSF diversion is yet to be considered an evidence-based established practice. The true benefit of this decision should be weighed with the risks prior to intrathecal access.

Meningitis

Development of postoperative meningitis is the primary concern in the setting of CSF rhinorrhea (though chronic positional headaches and nasal drainage are also of concern). Fortunately, the incidence of postoperative meningitis remains relatively low (0–5.7%; mean 1.8%) [13, 30, 56–62]. Kaptain et al. reported a comprehensive review of series reporting CSF leak and meningitis rates [42]. The most notable finding is that there were significantly fewer patients who developed meningitis even with postoperative CSF leaks. In our experience (unpublished) of 681 patients, only six developed bacterial meningitis (0.9%) and none of these patients had postoperative CSF rhinorrhea. Rather, duration of surgery and comorbidities (Cushing disease with uncontrolled diabetes) were associated risk factors.

Hypopituitarism

Postoperative pituitary dysfunction varies tremendously depending on pathology, tumor size, and presenting conditions [21, 63]. For pituitary adenomas in particular, probably the most important risk factor for new hormonal dysfunction is increasing tumor size [63]. Hence, it is challenging to categorize these as major complications. Nevertheless, patients who have experienced panhypopituitarism or permanent diabetes insipidus have notably diminished quality of life, rely on frequent hormone dosage adjustments, and can even develop functional urinary incontinence as a result [4, 5]. Hence, a discussion of such outcomes is warranted in any complications review.

Diabetes Insipidus

Reported rates of postoperative DI range from 2% to 4% in most large pituitary adenoma series [21, 64]. There is a wider range of DI following RCC and craniopharyngioma surgery (2% and 35% respectively). Hence, the pathophysiology of the tumor and the goals of surgery (gross total resection versus subtotal resection) can affect posterior gland function. In some cases, the infundibulum is deliberately transected to achieve GTR and avoid traction on the hypothalamus.

There is a notably higher rate of transient DI relative to permanent DI following pituitary surgery (8–24%) [21, 65–67]. This is a well-recognized sequela, which is carefully monitored and treated when appropriate. However, the reported rates vary partly due to the definition of transient DI (increased urination with or without hypernatremia, sodium level thresholds, necessity of DDAVP, etc.). Additionally, there is no consensus as to the accepted duration of this transient nature. Many articles set an arbitrary period of 3–6 months following surgery, though DI has been seen to resolve upwards of 2 years after surgery. Hence, studies with shorter follow-up periods may report artificially higher rates of DI.

SIADH

SIADH (or delayed hyponatremia) is also a well-recognized sequela following transsphenoidal surgery, with symptomatic hyponatremia occurring in approximately 5% of patients, most commonly between 5 and 7 days after surgery [8, 68]. This has been well studied and no obvious tumor characteristic has yet been proven to be associated with a higher rate of SIADH (tumor size, pathology, location, etc.). SIADH is the most common diagnosis for early postoperative readmission in transsphenoidal surgery patients [69]. When diagnosed and treated appropriately, there is no lasting effect on the patient. However, if hyponatremia is not detected in a timely manner, severe complications have been reported, including seizures, coma, and death [8, 70]. Many pituitary surgeons have adopted a routine delayed postoperative sodium level assessment for early SIADH diagnosis and treatment. Nuances of this management are discussed in the section "Minor Complications."

Anterior Gland Dysfunction

Anterior pituitary gland dysfunction is seen in a large portion of patients with pituitary macroadenomas and other pathology causing pituitary gland dysfunction. The degree of pituitary gland compression as well as the duration of endocrinopathy can affect postoperative outcomes. The incidence of new anterior pituitary dysfunction in any axis has been reported in up to 40% of operations (excluding total hypophysectomy), though most studies report ~5–9% dysfunction rates [21, 65, 71–73]. This has been shown to be directly correlated with pituitary tumor size with

giant macroadenomas associated with 15% dysfunction [21]. When the gland is markedly splayed and thinned over the adenoma, and partially obstructing access, we advocate a gland incision technique to prevent pituitary gland traction; this technique has been shown to preserve function [65].

"Minor" Endocrine Issues

Hormonal assessment is essential for pituitary surgery patients. A thorough understanding of preoperative pituitary dysfunction is necessary for positive surgical outcomes. Patients with hypocortisolism require preoperative and intraoperative "stress-doses" of corticosteroids to help their bodies cope with the operation and postoperative period [74]. These corticosteroids should be tapered based on the severity of the patient's deficiency and the condition of the patient. In patients with normal preoperative adrenal function, routine fasting morning cortisol assessment is necessary to diagnose postoperative adrenal insufficiency, which requires urgent cortisol replacement to prevent Addisonian crisis. In select patients with early recovery of their preoperative adrenal deficits, corticosteroid overdosage can occur with resultant hypertension, hyperglycemia, and psychosis. Again, early detection of this syndrome is necessary for good outcomes. Occasionally, cortisol measurement is altered by the administration of postoperative dexamethasone to prevent anesthetic-induced nausea or vomiting [75, 76]. Direct dialogue with the anesthesiologist is necessary to avoid this confounding event.

In patients with multiple pituitary axis failure, it is critical to avoid thyroid replenishment before cortisol replacement [77]. In this specific setting, as metabolic demands increase as a result of thyroid therapy, patients can develop severe cortisol depletion, which can be manifested by hypotension and Addisonian shock.

Following pituitary surgery, thyroid function is difficult or impossible to assess based on TSH alone [78]. Thyroid function should be assessed based on T3, T4, and TSH levels as well as the patient's clinical status.

Fluid and Sodium Issues

All postoperative pituitary tumor patients require routine and frequent endocrinological evaluations, specifically to diagnose diabetes insipidus (DI) and hypocortisolism (adrenal insufficiency). Strict fluid measurements are recorded; daily body weights are assessed; sodium levels, cortisol levels, and other pertinent hormone levels are measured. Various nursing and patient actions can interrupt this delicate postoperative balance. Fluid and sodium measurement is necessary for the early diagnosis of DI and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [75, 79, 80]. Overhydration of these patients can result in false hyponatremia resulting in premature SIADH therapy. We encourage patients to drink only to thirst when they exhibit signs of DI; otherwise, water pitchers and free access to fluids are strictly forbidden.

Conversely, the overadministration of DDAVP (desmopressin) can result in fluid retention and severe hyponatremia [81, 82]. Typically, postoperative DI is mild and

can be managed by patient compensation via the thirst response. This tends to resolve within a week, and patients should be instructed to monitor their thirst and urination [79]. Patients discharged with around-the-clock DDAVP can return to the hospital with severe hyponatremia, sometimes with deleterious consequences. Certainly, patients with severe DI may require scheduled, multiple daily doses, but their fluid management should be frequently assessed. In our practice, we routinely obtain postoperative sodium levels on approximately the 5th–6th postoperative day to identify potential patients developing delayed SIADH that typically occurs between the 5th and 7th postoperative day. It can also help monitor the management of DI therapy, assisting with appropriate DDAVP administration and dosing. Patients with acromegaly in remission after surgery may develop transient excessive urination simulating DI as they mobilize acromegaly-related edema fluid from their tissues.

Minor Complications

Despite a well-executed operation achieving a complete tumor resection without major surgical complications, the outcome can be tainted by problems that are not directly related to the surgery or by what are considered "minor" complications. In fact, Ciric et al. reported that surgeons with greater experience in performing transsphenoidal surgery were more likely to have encountered a wider array of complications [30]. Relatively "minor" issues may even precipitate hospital readmission or reoperation (e.g. an abdominal fat donor site abscess). Furthermore, they detract from the patient's surgical experience; increase the cost of medical care, and in certain cases may lead to chronic and nagging issues for the patient. A list of possible complications, both major and "minor," can be found in Table 19.2a, b.

Anesthesia-Related Complications

The surgical pause and preoperative "time out" facilitate the prevention of complications and build team synergy. This is a critical time to review medications being given to the patient and key steps of the procedure that may have increased risk and to confirm availability of equipment and disposable needs.

Invasive Catheters

Disconnected or dislodged catheters can result in decreased administration of medications or infiltration into the extremity. Superficial thrombophlebitis can occur in as many as 25–35% of patients and may even propagate, leading to deep vein thrombosis (DVT) [83–86]. In the postoperative setting, one must remove redundant peripheral IV catheters, particularly those placed in the lower extremities. Early identification of a phlebitis and treatment with the appropriate antibiotics, nonsteroidal anti-inflammatory agents, or anticoagulants may be required. Elevation of the affected limb is effective to improve venous congestion [87].

Table 19.2 (**a**) Common major complications of transsphenoidal surgery. (**b**) Tabulation of minor complications of transsphenoidal surgery

Major complications
Vascular injury
Stroke
Visual loss or diplopia
DVT/PE (major)
Meningitis
Tumor bed hematoma
CSF rhinorrhea
Tension pneumocephalus
Hypopituitarism
Diabetes insipidus/SIADH
Epistaxis
Myocardial infarction
Pneumonia

Minor complications		
Anesthesia-related issues	*Sinonasal complications*	*Endocrine-related issues*
Invasive catheter complications	Alar injuries	Transient diabetes insipidus
ET tube malpositioning/Dislocation	Nasal burns	Delayed SIADH
Urinary catheter complications	Posterior epistaxis	DDAVP-induced hyponatremia
Oropharyngeal trauma	Anosmia/Dysosmia	
Medication reactions/allergies	Dyseguesia	
Corneal abrasions	Chronic sinusitis	
	Mucocoeles	*CSF diversion complications*
Positioning-related issues	Septal perforations	Intracranial hypotension
Three-point fixation complications	Cosmetic deformities	Retained lumbar drain catheter
Headrest “horseshoe” complications	(Saddle nose)	Radiculopathy
Oral complications	*Fat graft site complications*	
Pharyngeal abrasion	Abscess	
Hemoptysis (blood rundown)	Seroma	
Palatal/Dental hypesthesia	Wound compromise	

SIADH syndrome of inappropriate antidiuretic hormone secretion, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *CSF* cerebrospinal fluid

In specific cases, placement of more invasive catheters, such as arterial catheters and central venous lines, may be necessary. Radial arterial catheters can be complicated by vascular insufficiency causing digit or hand necrosis (0.09%) [88]. Central lines have a comparatively high infection rate and can be complicated by

pneumothorax, hemothorax, and cardiac arrhythmias [89, 90]. The best method to prevent these issues, in addition to proper sterile technique, is to avoid the placement of these devices altogether if not needed. For most lesions approached via the transsphenoidal route, the likelihood of significant blood loss or intracranial pressure considerations is low, negating the requirement for these invasive devices. Central venous and arterial catheters should generally be reserved for patients with significant cardiac or pulmonary comorbidities, as well as giant or invasive tumors with higher potential for arterial injury or significant blood loss.

Airway Issues

Airway management in transsphenoidal surgery can be challenging because of the various neck and head manipulations performed after intubation, which can result in migration or dislodgment of the endotracheal tube [30, 75]. This can result in distal displacement to the mainstem bronchus or proximal displacement into the larynx or even extubation. These conditions should be treated immediately and can be prevented with re-evaluation of endotracheal tube position and taping, lung sounds, airway pressures, and tidal volumes following the positioning of the patient's head. The simple maneuver of securing the endotracheal tube to the left side of the mouth and jaw (for a right-sided approach) allows for the tube to be in a more neutral trajectory to the trachea and prevents disruption of the airway circuit after the operation has begun [91, 92]. Additionally, disease-specific conditions can affect airway management. It is well established that patients with acromegaly, with macroglossia, pharyngeal mucosal redundancy, and prognathism, may present a challenge for laryngeal intubation [93, 94]. Frequently, fiberoptic intubation is necessary [95, 96]. Patients with Cushing disease are often obese, contributing to more difficult airway management and to problems related to increased intra-abdominal, intrathoracic, and central venous pressure [97]. Some of these are mitigated by positioning with the patient's thorax elevated 25°–30°.

Urinary Catheters

In many institutions, it has become standard practice to place Foley catheters in patients undergoing transsphenoidal pituitary surgery for intraoperative fluid management and postoperative fluid output monitoring – particularly in the presence of diabetes insipidus. As any invasive device, Foley catheters are associated with a low, but significant, rate of morbidity, including urinary tract infections, urethral trauma, and development of iatrogenic false passages [98–100]. The incidence of infection associated with short-term indwelling catheter use is approximately 5–10% [101, 102]. Intraoperative urological consultation may sometimes be necessary to place difficult catheters in patients with prostate hypertrophy and urethral strictures.

Prevention is the best medicine for these issues. It is reasonable to avoid placement of a urinary catheter in routine pituitary adenoma cases with anticipated

duration of up to 4 h, reserving placement only for longer cases, immobile patients, those with prior genito-urinary problems, or those with a history of postoperative urinary retention. Through patient and nursing education, accurate monitoring of fluid intake and output is still possible without Foley catheters. Known diabetes insipidus may require intraoperative urine output monitoring to manage fluid balance during the procedure. Conversely, urinary retention can be seen in patients in whom urinary catheters are not placed, particularly in older men with benign prostatic hypertrophy [103, 104]. This may necessitate delayed (and awake) placement of urinary catheters.

When a Foley catheter is inserted in the operating room, early removal of the catheter is prudent. This can help decrease the incidence of catheter-related infections. Simultaneously, it encourages the patient to ambulate early after surgery, which can decrease the patient's length of stay and potentially decrease the incidence of pulmonary complications or venous thromboses [105, 106]. Nevertheless, even a single straight catheterization is associated with infection; thus, once a catheter is inserted, it should be left in place until its use is no longer necessary [107].

Other Anesthesia-Related Issues

Numerous other "minor" issues have occurred that do not impact the overall surgical outcome, but can affect the patient's experience, the postoperative management, or the length of care. These can include the occasional devitalized, displaced, or chipped tooth; oropharyngeal irritation or tongue trauma; and intubation-related hoarseness and sore throat [108, 109].

Rarely, intraoperative medication reactions can jeopardize or abort the operation [110, 111]. In our recent experience, operations for two patients were aborted prior to tumor resection. One patient with no known medication allergies developed anaphylactic shock due to a cephalosporin antibiotic. Another patient with a known cardiac history developed blood pressure lability and electrocardiogram changes soon after induction, requiring rapid termination of the operation. Both patients underwent a successful second operation after their problems were resolved.

Frequently, ophthalmic lubricant is placed prior to securing the eyelids for eye protection to protect against corneal abrasion. Occasionally, these patients awake with complaints of "worse" vision that sometimes can trigger the performance of further diagnostic studies. Typically, these effects resolve spontaneously within 24 h or when washed with saline eye irrigation. Rarely, patients can develop a reaction to the eye lubricant resulting in scleral injection and reactive conjunctivitis. Conversely, if the eyes are not protected, patients can sustain corneal abrasions due to dessication, inadvertent intraoperative manipulation, or postoperative scratching by the patient (10% without protection compared with 3.3% with ophthalmic lubricant) [112, 113].

Positioning-Related Issues

Inadequate patient positioning in the neurosurgical operating room can significantly affect surgical outcomes. In our practice, the patient is positioned in a "beach-chair" position with the head tilted away from the surgeon to allow for a comfortable operating angle; the head is immobilized in either three-point fixation or more commonly with a horseshoe head holder. With either method, neuronavigation can be employed. With three-point fixation, the most common complaints are pin-site pain and headaches [114]. Despite preoperative counseling, patients may be surprised to have pin-site discomfort and find that the pain is often more severe than the operative site pain. The incidence of this source of pain has not been quantified in the neurosurgical literature. Other complications of three-point fixation include pin-site lacerations, direct cutaneous nerve injury, and epidural hematomas, all of which can be prevented with careful pin application [115, 116].

The horseshoe head rest allows for increased mobility and maneuverability during the operation and precludes the issues of pin-site pain or bleeding, but may be less secure. In lengthy operations, the use of horseshoe positioning can be associated with scalp maceration, ischemic ulcers, and alopecia. This postoperative pressure-related alopecia has been reported in head and neck surgery, cardiac surgery, and gynecological surgery, but to our knowledge has not yet been reported with transsphenoidal surgery [117, 118]. This complication can be avoided with the use of three-point fixation for operations that are likely to last more than 5 or 6 h.

Sinonasal Complications

Depending on the approach for transsphenoidal surgery, various nasal comorbidities can be encountered (Table 19.2b). Speculum-assisted microscopic approaches can be associated with alar ring tears and nasal burns when using monopolar electrocautery [119–121]. Monitoring the alar skin during speculum distraction can decrease the incidence of these injuries. Anterior nasal septal perforation is a recognized complication and has been reported in approximately 7% of transsphenoidal operations [9]. The incidence of septal perforations has decreased as surgeons have converted from the sublabial transseptal approach to direct endonasal approaches (microscopic or endoscopic) [122, 123]. Additionally, deep placement and vigorous opening of the speculum blades can potentially damage the hard palate, the optic canals, or the carotid arteries with rare but serious catastrophic outcomes [14, 30]. Postoperative numbness of the anterior teeth and palate can occur as a result of dissection and cautery during the exposure. These maneuvers may also result in a loss or distortion of the senses of smell and taste.

As the use of an endoscopic approach has proliferated, increased mucosal trauma and dissection has resulted in various untoward outcomes. Aside from the noted major complication of posterior nasal epistaxis, various other complications include anosmia, dysosmia, dysguesia, chronic sinusitis, mucocoele, synechia development, and nasal burns [124]. Violation of the superior olfactory strip (SOS) during

the posterior nasal dissection can result in anosmia, dysosmia, and resultant dysguesia [125, 126]. These symptoms typically resolve over time (2–3 months) but can be persistent in a minority of patients [126, 127]. Avoiding resection or damage to the SOS can help prevent persistent anosmia or dysosmia [44]. With larger exposures, synechiae and mucocoeles can develop over time and can result in airway obstruction or chronic sinusitis. Frequent postoperative irrigation and routine endoscopic debridements can help prevent these outcomes. A close relationship with otorhinolaryngologists can help with the prevention, early diagnosis, and treatment of these problems. On rare occasions a cosmetic deformity of the nose ("saddle nose") or the distal nasal septum may occur and may warrant surgical correction.

With the increasing use of the nasoseptal flap for closure when a major CSF leak is present, one must anticipate problems related to the creation and management of the flap. The denuded side of the septum may heal poorly, become encrusted, or even be colonized by bacteria. The flap itself may become twisted on its pedicle or otherwise develop devitalization and necrosis. Care in both obtaining and applying the flap and in following its progress in healing is essential to success.

Bone, cartilage, or artificial materials used to reconstruct the sella, if not securely seated, may extrude through the nose in the postoperative period. Most commonly, this is a nuisance to the patient. However, in the early postoperative period, this can result in the failure of the CSF leak repair and subsequent CSF rhinorrhea.

When the nares are packed as part of the closure, it is important to remember that the patient must remain on antibiotics while the flap is in place in order to avoid a potential toxic shock situation.

Rarely, the endoscope itself can cause soft-tissue injury. The heat from the light source can result in tissue burns. If the endoscope is adjacent to the nasal skin at a high light intensity level for a prolonged period of time, significant cosmetic burns can occur. These can be prevented with a lower light setting and frequent variation of the endoscope location [128]. It is pertinent to remember that the endoscope's bright light can potentially ignite the surgical drapes resulting in an operating room fire [129]. The endoscope light intensity should always be decreased when not in use, and the tip of the endoscope should be moved away from the drapes. An astute surgical technician can help prevent these rare events.

Oral Complications

The most common oral complication associated with transsphenoidal surgery is palatal and pharyngeal abrasion from the use of throat packs. These can cause notable morbidity to patients, with pain sometimes worse than the operative site. We routinely avoid the placement of throat packs. The excess blood run-down is aspirated from the patient's stomach with the use of an oral-gastric tube placed during induction, along with compulsive cleansing of the operative approach and the choanae. Aspiration of this blood can help decrease the incidence of postoperative nausea, vomiting, and retching that could result in the failure of a CSF leak closure. Other, less common

oral complications include palatal and dental numbness from nerve disruption. This is most commonly seen with the sublabial approach, but has been reported with endonasal approaches as well [75, 130]. Maintaining the mucosal attachments at the anterior nasal region can help prevent this outcome.

Fat Graft Harvest Site Complications

Abdominal fat graft site complications may include wound breakdown, infection, hematoma, and poor cosmetic outcome. These are all typically avoidable with use of meticulous surgical technique [131]. Incision site infections are typically seen with poor dissection technique and imperfect incision closure. Overuse of monopolar electrocautery can result in devascularization of the harvest site and wound breakdown [132]. In our practice, the fat is typically harvested from the right lower quadrant with blunt and sharp dissection with Metzenbaum scissors. Electrocautery is reserved for spot cauterization of bleeding vessels to minimize the risk of postoperative hematoma and seroma. Careful skin closure of only the subcutaneous layer and avoiding deep stitches (Fig. 19.9) will reliably yield a cosmetically acceptable outcome.

Conclusions

Complications, both major and minor, are inherent with pituitary surgery. Early recognition and management are necessary to prevent worsened outcomes, though prevention is certainly the best approach for most potential complications. A technically perfect operation using any surgical approach can be negated by "minor" complications. These are unique events and can be unfamiliar to the inexperienced pituitary surgical team. Each issue, if left untreated or mismanaged, can result in significant and potentially life-threatening harm to the patient. Rigorous and detail-oriented intraoperative and perioperative care can help prevent these outcomes. The "devil" may be in the details, but the onus lies with the surgeon and his team to avoid both major and minor complications.

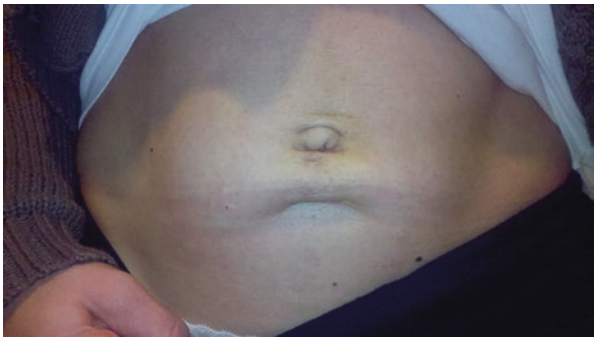

Fig. 19.9 Postoperative fat graft wound deformity. This resulted from a deep stitch placed to close the "dead space." The patient was taken back to surgery 4 weeks postoperatively to revise the wound

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Rhinological Complications: Avoidance and Management

20

Gustavo J. Almodovar-Mercador, Theodore H. Schwartz, and Vijay K. Anand

The endoscopic transsphenoidal approach is becoming the technique of choice for accessing sellar, parasellar, and anterior skull base pathologies. This expanding role of endonasal skull base surgery is the result of concerted effort to prevent and manage peri- and postoperative complications. Although complications may be inherent in any surgical procedure, they are best prevented rather than treated.

Rhinological complications in endoscopic transsphenoidal surgery can be similar in nature to those encountered during traditional endoscopic sinus surgery and can negatively impact the patient's long-term quality of life. To help minimize potential complications, it is of paramount importance to have the knowledge and training required for understanding the endoscopic anatomy and employing this technique [1]. Important points to consider when planning this approach may include meticulous review of preoperative imaging studies for correlation with anatomical landmarks and use of these for image guidance intraoperatively. Methods utilized include mucosa-sparing surgical technique, knowledge of the relationship of the sphenoid sinus septations with respect to the carotid arteries, use of intrathecal fluorescein for identification of intraoperative cerebrospinal fluid (CSF) leaks, and conscientious postoperative care with frequent debridement and nasal toilet until the skull base is completely healed [2].

G.J. Almodovar-Mercador, MD
Assistant Professor, Rhinology and Endoscopic Skull Base Surgery Otolaryngology-Head and Neck Surgery, University of Puerto Rico, School of Medicine, New York, NY, USA

T.H. Schwartz, MD
Department of Neurosurgery, Weill Cornell Medical College,
New York Presbyterian Hospital, New York, NY, USA
e-mail: schwarh@med.cornell.edu

V.K. Anand, MD (✉)
Department of Otolaryngology and Head and Neck Surgery, Weill Cornell Medical College,
The New York Presbyterian Hospital-Weill Cornell Medical Center, New York, NY, USA
e-mail: vijayanandmd@aol.com

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_20

In this chapter, we present the most common and critical rhinological complications during endoscopic transsphenoidal surgery: (a) immediate complications, such as vascular injury during the approach, intraoperative unplanned CSF leak, nasal vestibule burns that occur intraoperatively, and (b) delayed complications which can occur weeks to months after surgery, such as crusting, synechia formation, chronic sinusitis, mucocele, and loss of olfaction. The management of these complications and recommendations for their avoidance will be described in detail.

Perioperative Rhinological Management

The majority of patients undergoing endoscopic transsphenoidal surgery are admitted to the neurosurgical intensive care unit or the nursing ward in the immediate postoperative period for close observation and monitoring.

At our institution, telfa gauzes or absorbable nasal packings at the end of the procedure are placed in the nasal cavities to wick blood in the immediate postoperative period, and the packing is removed 24–48 h after the surgical procedure. Antibiotic prophylaxis is given preoperatively and continued until removal of nasal packing. The head of the bed is kept elevated up to 30° from the supine position. Ice packs are placed around the nose and face as needed for pain and pressure relief. Mist humidification to the sinonasal cavity can be given through a face tent. Oxygen delivery through nasal cannulas should be avoided in the postoperative period to reduce drying of the nasal mucosa and to prevent the potential of causing tension pneumocephalus, which is a devastating complication [3]. Nasal sprays and irrigations should be carefully used during the first postoperative week because they may cause bleeding or displace materials used for reconstruction of the skull base.

Patients are instructed to avoid nose blowing, sneezing with the mouth closed, drinking through straws, and heavy lifting or strenuous activities involving maneuvers that may increase intracranial pressure, thus minimizing the risk of a cerebrospinal (CSF) leak. They should also adhere to a bowel regimen of stool softeners and be discharged with antibiotic and pain control medications. A follow-up appointment with the otolaryngologist can be given 1 week after discharge.

Immediate Rhinological Complications

Vascular Perioperative Complications

During endoscopic transsphenoidal surgery, meticulous hemostasis during the approach phase is imperative in order to maintain adequate visualization for the dissection portion of the procedure and to prevent postoperative vascular complications. Detailed study of the paranasal sinus and anterior skull base anatomy, including its neurovascular anatomy on preoperative imaging (CT, MRI, and computed tomography angiography [CTA]) and availability of tools such as image guidance, are important to prevent catastrophic intraoperative vascular injuries. The spectrum of bleeding during the approach phase ranges from minor nasal mucosal

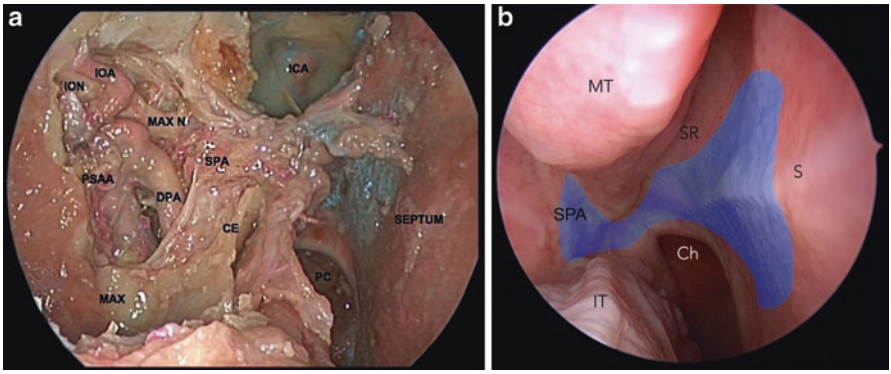

Fig. 20.1 (**a**) Anatomical dissection of the right pterygomaxillary space. Sphenopalatine artery (*SPA*) seen posterior to the posterior maxillary sinus (*MAX*) wall and superior to the crista ethmoidalis process (*CE*) of the palatine bone. (**b**) Nasal endoscopy of right nasal cavity. Possible location of SPA in the posterior nasal cavity shaded in blue

bleeding to pulsatile arterial bleeding from a moderate-sized vessel, such as the sphenopalatine artery.

The sphenopalatine artery, a branch of the maxillary artery and part of the external carotid artery system, reaches the nasal cavity through the sphenopalatine foramen, which is located anterior to the attachment of the middle turbinate, just posterior to the posterosuperior border of the maxillary sinus and superior to the crista ethmoidalis process of the palatine bone (Fig. 20.1a, b). This artery is frequently manipulated during the approach in endoscopic transsphenoidal surgery. Arterial hemorrhage may be caused from direct injury to the main trunk of this artery or to its terminal branches: the septal branch and the posterior nasal branch. These branches may be lacerated accidentally, respectively, during enlargement of the sphenoid sinus rostrum or at the tail of the middle turbinate when performing a middle turbinectomy if indicated. This can be avoided by not extending too far inferior and laterally during removal of the mucosa and soft tissue underlying the sphenoid sinus rostrum. "Rescue flap" techniques that preserve the mucosa containing the nasal-septal vascular pedicles in cases in which a nasoseptal flap (NSF) is not used for reconstruction have been described [4, 5].

Several surgical techniques have evolved in the attempt to manage intraoperative bleeding and to prevent postoperative hemorrhage [6]. Nasal mucosal bleeding can be managed with topical thrombin with epinephrine, monopolar/bipolar cautery, warm water irrigation (110° F), and/or a variety of hemostatic agents. In all cases, bleeding of the main trunk or branches of the sphenopalatine artery requires meticulous coagulation of the vessel either with monopolar or bipolar cautery or in clipping. Meticulous hemostasis is done not only to stop the active blood loss but also to prevent possible delayed epistaxis.

Minor postoperative nasal bleeding is expected and infrequently requires any invasive treatment. Most can be controlled with mist humidification and changes of the nasal dressing as needed to avoid vestibular nasal crusting. If bleeding is moderate or severe, it may be controlled with a hemostatic matrix or intranasal packing.

Endoscopic visualization of the bleeding site is recommended for direct effective hemostasis and to avoid damage to the skull base reconstruction. In a cooperative patient, local anesthesia and electrocautery can be applied under endoscopic guidance to control the bleeding in the immediate postoperative period. These measures, however, may be impractical if brisk bleeding occurs in the immediate postoperative period. During these circumstances, if the source is not clearly visualized, compressive packing may be utilized, and controlling the hemorrhage in the operating room is recommended. This is particularly critical in the immediate postoperative period given the higher risk of displacing the skull base reconstruction and the possibility of an unidentified intracranial source of bleeding [7]. Delayed epistaxis after undergoing endoscopic transsphenoidal surgery occasionally occurs. A recent database review of 466 patients who underwent this procedure in a tertiary care center by Hendricks et al. showed that only 2.1% of the 30-day readmissions were for epistaxis. If it occurs, management should follow the previously described care depending on the severity of the bleeding [8].

Intraoperative Unplanned Cerebrospinal Fluid Leak

An unintended skull base defect iatrogenically created during the approach phase of endoscopic transsphenoidal surgery can occur in a similar fashion as those that can occur during endoscopic sinus surgery. It is important to apply the same rigorous concept of sinus surgery when working near the anterior cranial fossa structures. Special attention should be placed when lateralizing the turbinates as they can be attached to the skull base in their superior vertical portion. During posterior septectomy, it is first recommended to initiate the superior cut of the perpendicular plate of the ethmoid bone owning to its continuous connection with the cribriform plate. Another area of possible injury during opening of the sphenoid sinus rostrum is the planum sphenoidale. Inadvertent forceful manipulation applied in these areas can cause a skull base defect with resultant low-flow CSF leak.

A low-flow CSF leak is considered to be one that does not disrupt a cistern or ventricle. Its identification is critical, and it may go unnoticed because of poor visualization in the operative field. Intrathecal fluorescein is a useful tool for the identification of such intraoperative CSF leaks. In our institution, we recommend a dosage of 0.25 mL of injectable 10% fluorescein solution mixed in 10 mL of CSF [2]. Patients should first be premedicated with diphenhydramine (50 mg intravenously) and dexamethasone (10 mg intravenously) to reduce the risk of inflammatory or allergic reaction. The use of intrathecal fluorescein represents an off-label use of the product and requires informed consent discussion with the patient. Previous publications of our group have demonstrated the efficacy and safety of intrathecal fluorescein [9, 10].

Techniques for closure of these CSF leaks are similar to the type of closure used when repairing a CSF leak for iatrogenic defect created during a sinus surgery complication. The techniques may include insertion of a fat graft or a multilayered reconstruction. Typically, this includes placement of an inlay graft, which is usually placed in the epidural space, followed by an onlay graft supported by nasal packing. Options for the inlay graft include bone, cartilage, or synthetic dural substitutes

(such as DuraMatrix, Durepair®, Medtronic Inc.). A free mucosal graft, which can be obtained from a resected middle turbinate, the septum, the inferior turbinate, or the nasal floor, are good options for an onlay graft. The use of autologous abdominal fat and cadaveric acellular tissue (eg, AlloDerm®, Lifecell Inc.) has also been described for anterior and middle cranial fossa skull base defects. A vascularized nasoseptal flap can also be used in larger defects.

Nasal Vestibule Burns

The nasal vestibule and nostrils are at risk of superficial burns, pressure sores, and abrasions caused by the endoscope after prolonged cases. As rod-lens endoscope and other instruments used, such as drills and electrocautery, generate heat, continuous evaluation to avoid significant thermal injury is recommended. In the majority of cases, these conditions are self-limited and respond well to topical antibiotic ointment and local wound care, fortunately leaving no permanent sequelae.

Immediate Postoperative Cerebrospinal Fluid Leak

Most CSF leak closure failures present before patients are discharged from the hospital. Surgeons generally advocate managing early CSF leak initially conservatively with lumbar drain placement for 2–3 days, bed rest, elevation of the head of the bed, and a bowel regimen [11–14]. In our institutional series of 127 patients reported in 2007, the CSF leak rate was 8.7%. Of the 11 patients with leaks, 10 were managed conservatively and had resolution of the leak, not requiring additional surgery [11]. This technique is recommended only if a multilayered closure has been performed. A low rate of lumbar drainage outflow is recommended (5 mL/h) to avoid any risk of pneumocephalus and is indicated for 3–5 days. Serial CT scans should be used to monitor for the development of pneumocephalus [2].

Another option that has been advocated is that CSF leaks should be immediately explored and repaired, but giving an initial trial of CSF diversion [12, 15].

Postoperative Rhinological Management

Meticulous postoperative care is essential in the postoperative period to healing after endoscopic transsphenoidal surgery. All post surgical patients should be seen by the otolaryngologist one week post operatively for endoscopic wound care. At this initial appointment, the nasal cavity is conservatively debrided, which include removing crusting, old blood, mucoid secretions, and breakdown products of tissue and secondary to the use of hemostatic agents. In the first 2 weeks after surgery, the skull base should not be aggressively debrided because disruption of its repair can occur and this may precipitate a CSF leak. Careful inspection without instrumentation of the operative bed is performed to ensure that the field has remained uninfected. Any crusting along the reconstruction site is left in place until subsequent visits and removed if no

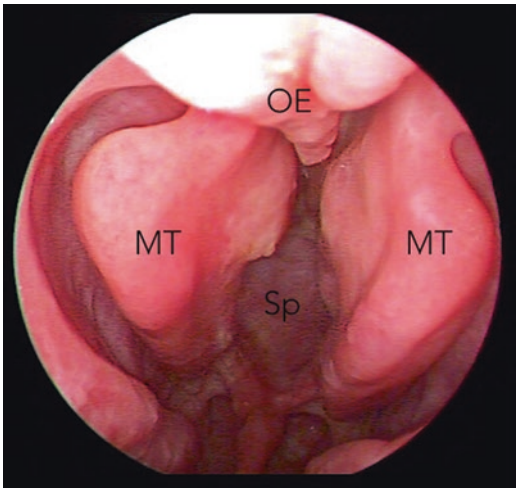

Fig. 20.2 Completely healed nasal cavity, sphenoid cavity (*Sp*), skull base, and olfactory mucosa (*OE*)

longer attached to the skull base. At this time, patients are placed on gentamicin nasal spray (80 mg gentamicin in 1000 mL normal saline) for 1 month. This has been shown to decrease bacterial colony counts and improve mucociliary function of the nasal and sinus cavities [16].

Patients are subsequently seen 2–3 weeks afterward and more aggressive debridement can be performed as needed during these appointments. Meningeal signs or symptoms as well as the presence of CSF rhinorrhea should always be evaluated in these follow-up appointments as well. Most of the patients have complete healing of the skull base by 6–12 weeks postoperatively (Fig. 20.2). Diligent postoperative care decreases the chance of infection, crusting, and the formation of synechiae.

Delayed Rhinological Complications

Crusting

Postoperative crusting is expected after endoscopic transsphenoidal procedures (Fig. 20.3). The combination of blood and necrotic tissue products, hemostatic material, dry mucus, mucosal damage, impaired mucociliary clearance, and bacteria that thrive in this environment constitute this initial formation of crusting. In a prospective cohort study of 63 patients, the authors found that the most common morbidity is nasal crusting, which was present in a majority of patients, with nearly half of the patients having moderate to severe crusting at 1 month postoperatively [17]. The median time to absence of nasal crusting in this cohort was 101.0 days. Patients who had a more complex approach had a significantly longer time to absence of nasal crusting than did those who had a simple approach (105.0 vs. 93.0 days; P 5 .033). The median time to remucosalization for patients with NSF was 89.0 days (95% CI, 72.7–105.3).

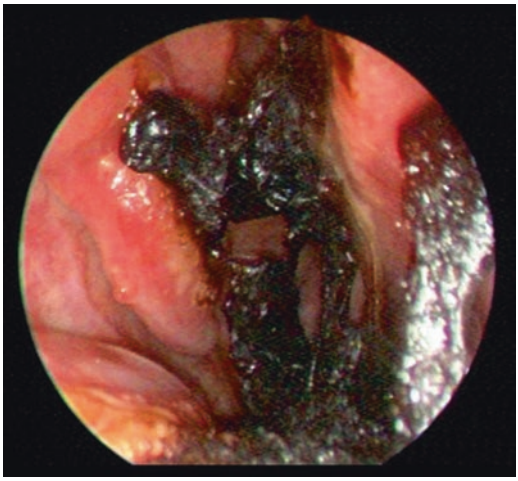

Fig. 20.3 Nasal cavity crusting after endoscopic skull base surgery

It is important to understand the timeline of these changes to provide education to patients about the expected postoperative course. Topical therapy with saline irrigation, antifungal topical sprays, antibiotic sprays, and mucolytics as well as postoperative debridements improve mucosal healing, encourage mucociliary function, and decrease synechia formation. The disadvantages of debridement include bleeding, mucosal avulsion, and minor discomfort. Several randomized, blinded clinical trials confirm that although patients undergoing debridement have additional bleeding and discomfort, they experience fewer synechiae and less nasal obstruction over time [18].

Synechiae

Despite meticulous surgical and postoperative care with debridements, postoperative synechia or scar tissue may occur in the sinonasal cavity after endoscopic pituitary and skull base surgery. Several randomized, blinded clinical trials confirm that although patients undergoing debridement have additional bleeding and discomfort, they experience fewer synechiae and less nasal obstruction over time [18].

Synechiae can commonly occur between the posterior nasal septum and middle turbinate/lateral nasal wall after endonasal, transsphenoidal approach to the sella (Fig. 20.4). More lateral approaches can result in synechia formation between the middle turbinate and lateral nasal wall. They can cause obstruction of nasal airflow and sinonasal drainage pathways, potentially causing rhinosinusitis. Lysis of synechia is important to avoid these further complications. The otolaryngologist may transect soft, early synechia under topical anesthesia in the early postoperative care and debridement. Solid, mature synechia requires a formal lysis of synechia with topical and local anesthesia followed by resection of scar tissue and placement of a spacer to avoid reformation of the synechia.

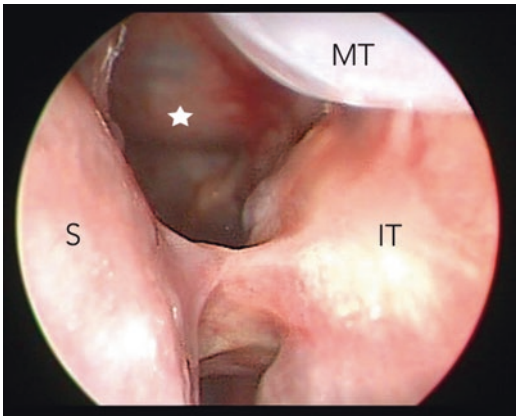

Fig. 20.4 Synechia formation between nasal septum (*S*) and left inferior turbinate (*IT*)

Postoperative Sinusitis

Chronic sinusitis is one of the most common diseases presenting in the United States. Evaluation and treatment of the paranasal sinuses are essential in the overall comprehensive management of patients with skull base lesions.

The preservation of sinonasal function requires careful preoperative evaluation of the sinuses. Optimizing the function of the sinuses preoperatively to allow for a safe surgical corridor to enter the intracranial cavity is of paramount importance. In patients with concomitant chronic rhinosinusitis with or without polyps, the paranasal sinuses can be surgically addressed at the same time as endoscopic skull base surgery [3, 19]. In some patients, sinus surgery may be necessary prior to the endoscopic skull base surgery to establish a stable mucosa for wound healing following the second skull base surgery [20].

Established principles in endoscopic sinus surgery for inflammatory disease should be applied to endoscopic transsphenoidal surgery. Meticulous intraoperative mucosal-sparing sharp dissection with preservation of sinonasal ostia and structures not directly involved with the pathology, with long-term follow-up postoperatively, are important factors for preventing future sinonasal complications. Using the meticulous techniques of endoscopic sinus surgery will help to promote sinonasal mucosal preservation and mucociliary clearance, maintain ostia patency, minimize crusting, and prevent scar formation [18, 21].

Mucosal stripping is avoided except in areas immediately around the skull base defect to allow the skull base reconstruction to adhere directly to the bony skull base. Permanent reconstructive materials, including nasoseptal flap, that cover mucosa are likely to result in mucocele formation and this must be avoided (Fig. 20.5). Otherwise, the mucosa should be preserved [22, 23].

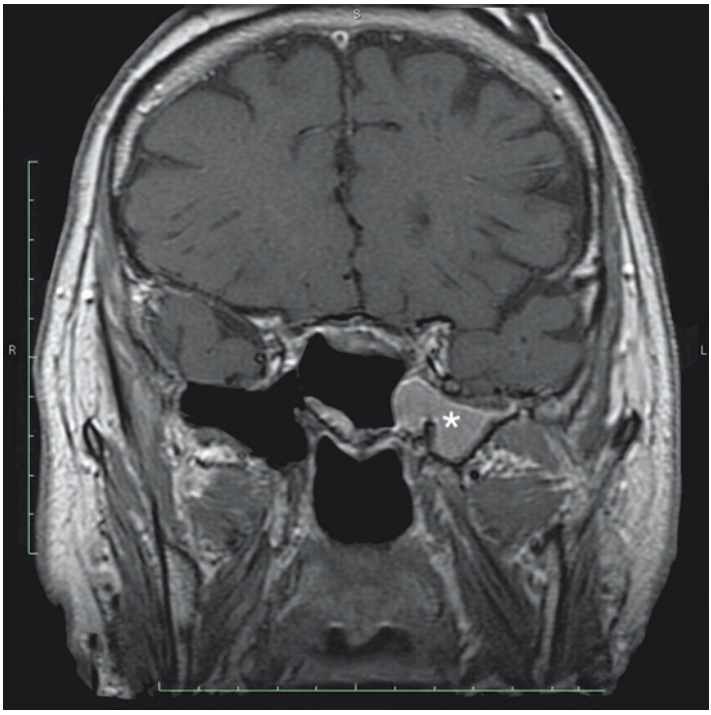

Fig. 20.5 T1-weighted gadolinium contrast-enhanced MRI of paranasal sinuses illustrating a mucocele formed (*star*) on the laterally pneumatized left sphenoid sinus after nasoseptal flap reconstruction for endoscopic skull base surgery

Acute Rhinosinusitis

Acute rhinosinusitis is unusual after endoscopic pituitary or skull base surgery. More common is crusting, accompanied with mucoid secretions without significant mucosal inflammation. Medical management with antibiotics is well supported in the literature to eradicate bacteria from the sinuses, hasten recovery, and improve quality of life [24]. Adjunctive treatments that include decongestants, corticosteroids, saline irrigation, and mucolytics may provide symptomatic relief to patients. Topical therapy, including nasal sprays and irrigation must be used cautiously in the immediate postoperative period to avoid disturbing the skull base reconstruction, specifically hastening the dissolution of dural and tissue sealants. Although amoxicillin is the first-line therapy for acute bacterial rhinosinusitis, this may not be the appropriate choice in patients after endoscopic skull base surgery. This may occur because these patients have received antibiotics while in the hospital, thereby increasing the potential of antibiotic-resistant bacteria. High-dose amoxicillin-clavulanate (4 g per day amoxicillin equivalent), a respiratory fluoroquinolone (levofloxacin, moxifloxacin), macrolides, or a third-generation cephalosporin (ceftriaxone) may be a better choice for antibiotic therapy in these patients [25].

Topical therapy, including nasal sprays and irrigation, encourages sinonasal healing but theoretically may displace the multilayer reconstruction and/or hasten the breakdown of dural and tissue sealants. As previously stated, postoperative surgical debridements must also proceed with significant caution given the risk of disturbing the skull base reconstruction.

Chronic Rhinosinusitis

Chronic rhinosinusitis in patients who had undergone endoscopic transsphenoidal surgery is usually limited to the sphenoid sinus (Fig. 20.6). It was found to be the most common delayed complication in a recent retrospective review of patients undergoing endoscopic resection of paranasal sinus or skull base neoplasm from 2007 to 2013 in a tertiary care center [26]. When present, it has been shown to be a predictor of lower quality of life in the postoperative course of these patients [27]. Common symptoms of isolated sphenoid sinusitis are retro-orbital and/or frontal headache, postnasal drip, nasal obstruction, epiphora, and/or fever [28]. The pathophysiology of sphenoid sinusitis in the postsurgical patient can comprise mechanical obstruction of the sphenoid drainage pathway, synechia formation, decreased mucociliary clearance, or mucocele formation.

As previously stated, it is recommended to use a minimally invasive approach with maximal preservation of normal intranasal structure and function. A meticulous mucosa-sparing technique is critical in the postoperative course of these patients because preserving as much normal mucosa as possible and only removing that which is necessary promotes healthy postoperative ciliary movement and an earlier reestablishment of mucociliary flow. With this approach, there is decreased crusting, synechiae, and obstruction of natural ostia. If a nasoseptal flap is harvested, alternatively, the mucosa from the sphenoid must be completely removed to assure that a mucocele does not form behind the flap. In most of the surgical approaches, it is not necessary to remove the middle turbinate and these can easily

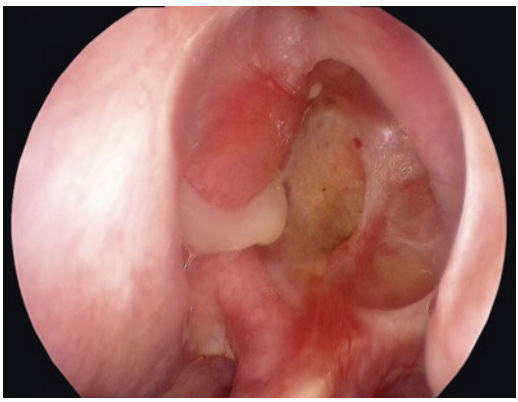

Fig. 20.6 Chronic sphenoethmoiditis with mucopurulent discharge

be preserved with simple lateralization. In certain extended transsphenoidal approaches, the superior, middle, or inferior turbinate may have to be removed to expose the skull base adequately.

Determining the exact incidence of postsurgical sinusitis following endoscopic transsphenoidal surgery can be difficult due to a small number of cases reported as well as differences in surgical approaches and closure materials used. The incidence has decreased to the 6–8% range in the most recent literature [29–31]. Most of these cases can be successfully treated medically with courses of antibiotics, topical antibiotics, and systemic or topical steroids, and are expected to resolve within 3 months. In cases where sinusitis persists and is refractory to over 2 months of medical therapy, risk of major neurologic or ophthalmologic complications increases or mucocele formation is noted. Endoscopic sinus surgery is recommended with enlargement of the sphenoid sinus ostia and removal of debris, marsupialization of mucocele if present, and restoration of drainage pathway.

Olfaction Loss

Anosmia, or loss of sense of smell, is the clinical consequence of bilateral damage to the olfactory nerves and/or of the resection of the neurosensorial olfactory mucosa. An additional complication associated with excessive mucosal sacrifice during an endonasal endoscopic approach is the destruction of the olfactory epithelium in the area of the olfactory mucosa, covering the cribriform plate, nasal septum, and medial wall of superior and middle turbinate [32, 33].

During the endoscopic transsphenoidal approach, avoidance of destruction of this mucosa should be maintained to preserve the olfaction, since its effect is permanent and irreparable. If elevation of a nasoseptal flap is planned, it is advised to incise the mucosa 1–2 cm below the superior most aspect of the septum in order to preserve the olfactory epithelium in this region when creating the posterior-superior limb of the flap as originally described by Hadad et al. [34] (Fig. 20.7). A smaller modified

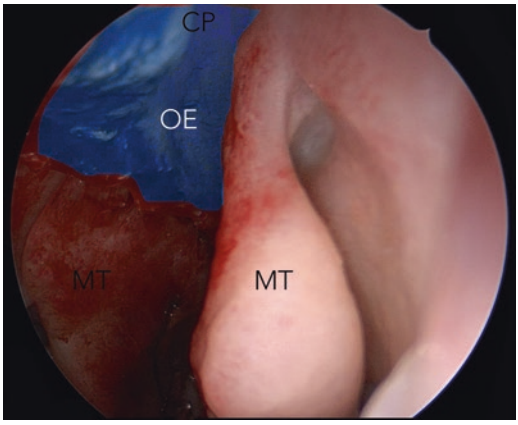

Fig. 20.7 Olfactory mucosa (*OE*, *blue shaded area*) preserved at superior nasal septum after harvesting of a nasoseptal flap. Note the location relationship to the vertical lamella of the middle turbinates (*MT*)

technique of this flap has been recently described, providing a low morbidity approach with no changes in olfaction at 6 months postsurgery and maintaining reconstruction options [35]. If no nasoseptal flap is planned or required for skull base reconstruction, then a unilateral or bilateral "rescue flap" technique that preserves the mucosa containing the nasal-septal vascular pedicles and the septal olfactory mucosa can be employed [4, 5]. Once the sphenoid ostium is identified, the mucoperiosteal incision is commenced inferior to the sphenoid ostium and extending laterally for a few millimeters. The incision is carried anteriorly and horizontally for approximately 2 cm along the perpendicular plate of the ethmoid and posterior nasal septum, and ending at a point opposite to the anterior most portion of the middle turbinate. It is then extended further anteriorly and superiorly in a hockey stick-shaped fashion to facilitate flap mobilization; this is the same superior incision used to raise the formal NSF and preserve the posterior-superior septal mucosa that contains much of the olfactory epithelium. Then, the procedure is repeated on the contralateral nasal cavity. These rescue flaps can be harvested fully if the resultant defect is larger than expected or if an unexpected CSF leak is encountered. Minimizing exposed bone and cartilage can reduce greatly the extent of crusting experienced postoperatively.

The current literature is conflicting on long-term olfactory outcomes after endoscopic skull base surgery. Several quality-of-life studies show that the majority of patients report a temporary, although significant, decrease in olfaction initially followed by a return to baseline functioning several months later [35–39]. On the contrary, other studies have shown decreased olfactory outcomes after endoscopic skull base surgery, especially if an extended approach is employed [39, 40].

Conclusion

Preventing, minimizing, and successfully managing complications with minimal morbidity and mortality remain paramount in endoscopic skull base surgery. Careful preservation of sinonasal structures is critical for minimizing intraoperative and postoperative rhinological complications after endoscopic skull base surgery. Meticulous postoperative care, with frequent nasal cavity debridement, and nasal toilet until the skull base is completely healed should be of utmost importance.

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Medical Management for Pituitary Adenoma Patients

21

Gregory K. Hong

Introduction

Medical management is a key component in the multidisciplinary care required by patients with pituitary adenomas. While transsphenoidal surgery often remains the first-line therapy for many pituitary adenomas, medical therapy often serves as an important adjunctive therapy. In the preoperative setting, medical therapy can lessen morbidity from tumor-induced hypopituitarism or from the adverse consequences of hormonal hypersecretion syndromes [1, 2]. In the postoperative setting, medical therapy reduces the morbidity associated with hypopituitarism [3] and is often necessary to control hormonal hypersecretion in cases of incomplete resection. In patients with prolactinoma, medical therapy is the first-line option; primary medical therapy can also be employed in Cushing's disease (CD) or acromegaly in patients who are not surgical candidates. Many pharmacologic options for treating hypersecreting pituitary adenomas exist, and a thorough understanding of their mechanisms of action, side effect profiles, and clinical use is paramount for the optimal care of a pituitary adenoma patient.

Background Physiology

Regulation of hormone secretion from the anterior pituitary is predominantly controlled by hypothalamic signaling mediators. Of particular note, prolactin (PRL) secretion is under negative tonic control by dopamine (DA) originating from the hypothalamus; any pathology that affects the pituitary stalk (e.g., surgical trauma, compression by tumor) and interrupts the transport of DA to the pituitary can result in

G.K. Hong, MD, PhD (✉)
Division of Endocrinology, Department of Medicine, University of Virginia Health System, Charlottesville, VA, USA
e-mail: gkh7z@virginia.edu

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_21

elevated prolactin. Inhibition of growth hormone (GH) secretion is also accomplished via somatostatin (SS) originating from the hypothalamus. While DA and SS are traditionally viewed as regulating only prolactin and GH secretion, it should be noted that many different anterior pituitary cell types express receptors for DA and/or SS. For example, various subsets of somatostatin receptors (SSTRs) are found not only in GH-producing adenomas but also in lactotroph adenomas, corticotroph adenomas, nonfunctioning adenomas (NFAs), and thyrotroph adenomas [4]. Similarly, while DA receptors are found at highest levels on prolactinomas [5], expression can also be demonstrated in some GH-producing adenomas, corticotroph adenomas, and NFAs [4]. The presence of these receptors in pituitary tumors is of therapeutic relevance as many of the medical therapies for pituitary adenomas rely on drugs which bind to the DA receptor or various subtypes of the SSTR. Indeed, resistance to medical therapy can often be correlated with decreased receptor number in the tumor or expression of different receptor subtypes [6].

Regulation of antidiuretic hormone (ADH) secretion from the posterior pituitary primarily occurs via input from vascular baroreceptors and hypothalamic osmoreceptors. Appropriate ADH secretion maintains blood volume and serum osmolality. Decreased ADH secretion from pituitary damage/pathology results in massive loss of free water from the kidney (central diabetes insipidus, DI). A syndrome of inappropriate ADH (SIADH) secretion frequently occurs after pituitary surgery and leads to excessive retention of free water, resulting in hyponatremia.

The clinical presentation of hypopituitarism or hypersecretion syndromes results from either deficiency or excess secretion, respectively, of pituitary hormones. An overview of the clinical manifestations of syndromes resulting from defective or unregulated pituitary hormone secretion is depicted in Table 21.1.

Hypopituitarism

Background and Diagnosis

Impairment of pituitary function occurs commonly with pituitary adenomas [7] and can result from mass effect of an enlarging tumor or from anterior pituitary (or stalk) damage during pituitary surgery. Furthermore, some hormonal hypersecretion syndromes cause impairment in the secretion of certain hormones from the anterior pituitary gland. For example, high cortisol levels seen in Cushing's disease inhibit gonadotropin release from the anterior pituitary resulting in hypogonadism [8]. Elevated PRL levels (either due to stalk compression or from a prolactinoma) will also inhibit gonadotropin release and lead to hypogonadism [9]. Hypopituitarism from pituitary tumors usually follows a characteristic sequence of loss, with GH deficiency being the most common, followed by gonadotropin deficiency, adrenocorticotropic hormone (ACTH) deficiency, then thyrotropin-stimulating hormone (TSH) deficiency [10]. Prolactin deficiency is rare and usually of no clinical significance.

Untreated hypopituitarism can result in significant morbidity and, in the case of central hypothyroidism or central adrenal insufficiency, mortality [11, 12].

Table 21.1 Clinical aspects of pituitary diseases

Syndrome	Manifestations/presentation	Comments
Adrenal insufficiency	↓wt, anorexia, malaise, GI upset, myalgias, hyponatremia	Necessary for life; adrenal crisis rare as aldosterone production preserved
Hypothyroidism	↑wt, cold intolerance, constipation, fatigue, myxedema coma (if severe and prolonged)	Necessary for life; manifestations identical to primary hypothyroidism
GH deficiency	Fatigue, ↓LBM, ↓bone density, ↑heart disease	Commonly seen with pituitary pathology
Hypogonadism	Amenorrhea, ↓sexual function, ↓bone density, ↓LBM (men)	Commonly seen with pituitary pathology
Diabetes insipidus (central)	Extreme thirst, polydipsia with polyuria (>3 L/d)	Rare with pituitary adenomas, more common with craniopharyngioma, infiltrative lesions, or metastatic disease
Prolactinoma	Hypogonadism, galactorrhea (usually in women only)	Males often present with mass effect symptoms due to later diagnosis
Cushing's disease	Centripetal obesity, facial plethora, hyperpigmentation, striae, mood lability, insomnia, proximal myopathy, hypogonadism, HTN, ↑A1c, coagulopathy	Manifestations occur along a spectrum; hyperandrogenism can occur in women due to ACTH-driven adrenal androgen production
Acromegaly	Soft tissue overgrowth, arthritis, sleep apnea, carpal tunnel syndrome, HTN, ↑A1c	Diagnosis usually delayed due to gradual onset of manifestations
TSH-oma	↓wt, palpitations, hyperdefecation, heat intolerance, goiter	Rare; characterized by elevated FT4 with normal (or elevated) TSH

Abbreviations: *wt* weight, *GI* gastrointestinal, *LBM* lean body mass, *HTN* hypertension, *ACTH* adrenocorticotropic hormone, *FT4* free T4, *TSH* thyrotropin-stimulating hormone

An evaluation for hypopituitarism is a key component of both the preoperative and the postoperative management of pituitary adenoma patients. Diagnosis of central hypothyroidism and central hypogonadism is straightforward and relies on demonstrating low levels of thyroid hormone or reproductive hormones with corresponding low (or inappropriately normal) levels of TSH or gonadotropins, respectively. In many cases, the diagnosis of hypogonadism in females can be made clinically from the history (e.g., new-onset amenorrhea). Diagnoses of ACTH and GH deficiencies are more complex; unequivocally low levels of ACTH and cortisol indicate central adrenal insufficiency, while a low insulin-like growth factor 1 (IGF-1) in the context of additional anterior pituitary hormone deficiencies usually indicates GH deficiency. Formal diagnosis of GH deficiency often requires documentation of a failure to stimulate GH secretion in response to insulin-induced hypoglycemia (a potent stimulator of GH release) [13]. Many experts use an 08:00 AM cortisol level of >10 μg/dL to indicate adequacy of the hypothalamic-pituitary-adrenal axis, although some studies report a sensitivity of only 62% for this test [14]. Formal stimulatory testing using cosyntropin (synthetic ACTH) should be pursued in patients with equivocal values or who have symptoms suggestive of adrenal insufficiency. It should be

recognized that this test relies on the development of chronic adrenal atrophy as a consequence of low ACTH levels over time; hence this test may not be valid in the immediate weeks (e.g., 4–6) after a pituitary surgery as the adrenal gland may not have significantly atrophied yet and may still be able to respond to a cosyntropin injection [15]. Hence even though a patient may have incurred pituitary damage during surgery, adrenal insufficiency would not be detectable in the immediate postoperative weeks using this testing strategy. In this situation, insulin-induced hypoglycemia can be utilized as a means of formally assessing the ability of the pituitary to secrete ACTH.

Posterior pituitary insufficiency leading to decreased ADH secretion and central DI only rarely occurs as a presenting feature of pituitary adenomas. However, pituitary adenoma patients may develop central DI, either temporarily or permanently, as a consequence of transsphenoidal resection (TSR) and the resulting damage to the pituitary stalk or posterior lobe [16]. While this diagnosis can be formally made with a water deprivation test [17], in many cases the diagnosis can be made on clinical grounds, i.e., persistent massive polyuria, thirst, and dilute urine in the postoperative setting.

Medical Treatment of Hypopituitary Patients

The primary goals of treatment of hypopituitarism are to minimize morbidity, decrease mortality, and improve quality of life through hormone replacement at physiologic levels [18]. Significant morbidity is a common feature of untreated hypopituitarism [19], and many studies (but not all) have demonstrated an increased mortality in hypopituitary patients [3]; it may be that inadequate or inappropriate hormone therapy contributes to increased mortality in this patient population. An overview of the usual treatment regimens employed in hypopituitarism is provided in Table 21.2; doses listed represent conservative starting doses, and dose titration upward will likely be required.

Replacement of glucocorticoid and thyroid hormones in a hypopituitary patient is of utmost importance as these hormones are essential for life; severe deficiencies in these hormones can be fatal in the context of a significant physiologic stress (e.g., adrenal insufficiency resulting in circulatory collapse following the induction of anesthesia) [20]. It is the author's preference to use hydrocortisone in twice-daily dosing (AM and late afternoon); dose requirements may be larger for patients with increased body surface area or increased weight [21]. It is rare for a patient to require more than 30 mg/day of hydrocortisone for physiologic replacement. A larger dose is given in the AM and a smaller dose is given in the late afternoon to mimic the normal diurnal variation of glucocorticoid secretion from the adrenal cortex (e.g., 15 mg upon awakening, 5 mg at 5 PM). Some patients will prefer a three-times-a-day dosing (e.g., 10/5/5), while others may feel well on a single daily dose; quality of life is likely similar in patients on different dosing regimens [22], although this is an area of controversy. Equivalent doses of prednisone or dexamethasone can also be used. It is the author's preference to avoid dexamethasone

Table 21.2 Management of hypopituitarism

Condition	Usual starting regimens	Monitoring
Adrenal insufficiency	Hydrocortisone 10–20 mg/d (divided twice daily) Prednisone 5 mg/d Dexamethasone 0.5–1 mg/d	Adjust dose based on clinical symptoms and signs of glucocorticoid excess/deficiency
Hypothyroidism	Levothyroxine 1.6 μg/kg ideal body weight (begin 25–50 μg/d in elderly or those with heart disease)	Adjust dose q4–6wks based on free T4 levels
Hypogonadism, male	Testosterone transdermal (40–60 mg/d) or IM (50–150 mg q14d)	Adjust dose q3mo to achieve total testosterone (or calculated free testosterone if SHBG abnormalities) within the normal range PSA (if >40yo) and CBC at baseline and 3mo following initiation/dose change; consider urologic referral if significant PSA rise
Hypogonadism, female	Oral contraceptive pills Transdermal estradiol (50–100 μg/24 h) plus intermittent progestin (e.g., medroxyprogesterone 10 mg/d x10d q1–3mo)	Can monitor and titrate based on serum estradiol level if on transdermal preparation; target level of 80–100 pg/ml
GH deficiency	Recombinant GH 0.2 mg sc daily	Adjust dose by (0.1 or 0.2 mg) q4–6wks based on IGF-1 levels (target IGF-1 in midrange of normal for age/sex)
Central DI	ddavp 0.05–0.1 mg PO BID (10–20 μg intranasally BID)	Adjust dose based on degree of polyuria

Abbreviations: *SHBG* sex-hormone-binding globulin, *PSA* prostate-specific antigen, *CBC* complete blood count, *GH* growth hormone, *IGF-1* insulin-like growth factor 1

given its long biologic half-life (>54 h) in order to minimize the possibility of iatrogenic Cushing's syndrome. The primary indicator of an adequate dosing regimen is the absence of symptoms/signs of adrenal insufficiency and glucocorticoid excess; routine biochemical monitoring of glucocorticoid levels is of no clinical benefit [23]. In general, the minimum dose of glucocorticoid that prevents symptoms of adrenal insufficiency should be used as glucocorticoid excess will have detrimental effects on metabolism (obesity, insulin resistance), reproduction (hypogonadism), and bone (osteoporosis), among others. Patients should be instructed to carry on their person information which identifies them as having adrenal insufficiency in the event of an emergency/trauma. For minor physiologic stressors (e.g., acute febrile illness), they are instructed to double their dose of replacement steroid for 48–72 h (or until clinical improvement is apparent). For trauma or major operative procedures (e.g., vascular surgery), they are given perioperative steroids at doses equivalent to cortisol output during times of severe stress, e.g., 100 mg hydrocortisone IV q8h [24]. Patients with nausea/vomiting who are unable to take their oral

glucocorticoid replacement can be prescribed an emergency supply of glucocorticoid to be given intramuscularly (e.g., 100 mg hydrocortisone in a vial, which can be reconstituted with sterile saline) and should seek emergency room care in order to receive injectable glucocorticoids. Rarely, initiation of glucocorticoid replacement therapy can unmask central diabetes insipidus due to increased vascular tone and improved renal blood flow promoted by adequate glucocorticoid therapy [25]; the onset of marked polyuria following the initiation of glucocorticoid therapy should alert the clinician to this possibility.

Thyroid hormone is typically replaced with oral formulations of thyroxine (e.g., levothyroxine), which is converted in the body by a deiodinase enzyme to the active form of thyroid hormone, triiodothyronine. Dosing requirements are dependent on the degree of residual endogenous thyroid hormone production in addition to body weight. Elderly individuals (i.e., >50) or those with known coronary artery disease are usually started at conservative doses with gradual dose titration upward given the theoretical risk of precipitating coronary ischemia by suddenly increasing cardiac output in a previously hypothyroid individual [26]. Adjustments in dosing are dictated by free T4 levels as TSH is unreliable in patients with pituitary damage; the goal is a normal free T4 level and the absence of symptoms/signs of hypo- or hyperthyroidism. Most patients with secondary hypothyroidism require between 50 and 200 μg/d of levothyroxine therapy. It is critical to note that in patients with concomitant hypothyroidism and adrenal insufficiency, replacement of thyroid hormone prior to the initiation of glucocorticoid therapy can result in adrenal crisis [27], presumably due to thyroid-hormone-mediated increase in cortisol metabolism. Hence in a patient with possible panhypopituitarism, replacement with levothyroxine should be undertaken only after the possibility of concomitant secondary adrenal insufficiency has been investigated. In patients with known panhypopituitarism, levothyroxine therapy should be started only after glucocorticoid therapy has been initiated.

Loss of sex steroid production is a relatively common occurrence in patients with pituitary adenomas and can result from the tumor itself (mass effect, hormonal hypersecretion in prolactinoma/CD) or as a consequence of pituitary surgery [10]. The most clinically significant consequences of hypogonadism are loss of fertility (in reproductive-age patients) and loss of bone density (with corresponding increased fracture risk) [28]. Treatment of hypogonadism in patients not desiring fertility involves direct replacement with either testosterone (for men) or estrogen/progesterone (for women). Testosterone is commonly administered via daily application of a topical gel which allows relatively constant levels of androgen. Alternatively, intramuscular testosterone can be used, which leads to peaks and troughs in serum testosterone levels but has the advantage of a markedly reduced cost. Given concerns over vascular risk [29], particularly in older men with equivocal total testosterone values, testosterone should be used only in men with unequivocally low values, taking into account the various factors that can influence sex-hormone-binding globulin (SHBG) levels (and hence influence the measurement of total testosterone levels) [30]. Potential side effects of treatment include erythrocytosis and a theoretical risk of increased growth of androgen-sensitive cancers; clinical guidelines recommend serial monitoring of complete blood count and prostate-specific antigen. The dose of testosterone should be titrated with a goal

target total testosterone in the midpoint of the normal range. In men with an SHBG at the extremes of the reference range, a calculated (or directly measured via LC/MS) free testosterone is likely a more valid monitoring parameter [31].

Estrogen replacement in women in the United States is most commonly achieved via oral or transdermal preparations. Oral contraceptive pills are often used to provide estrogen in young women or women at low risk of potential complications (e.g., venous thrombosis). Most modern oral contraceptive pills contain between 20 and 35 μg ethinyl estradiol (sufficient to prevent bone loss [32]) in combination with a progestin; progestin is necessary to prevent endometrial hyperplasia (a risk factor for endometrial cancer) from unopposed estrogen therapy. In women with risk factors for venous thrombosis, a transdermal preparation is preferred due to lower risk of thromboembolism [33]. Women on transdermal estradiol with an intact uterus also require progestin therapy for endometrial protection. Withdrawal bleeding after finishing a course of medroxyprogesterone usually indicates adequate estradiol levels.

Sex steroid replacement in patients with secondary hypogonadism desiring fertility is complex, costly, and often requires close monitoring under the supervision of a fertility specialist. An in-depth discussion of the possible regimens is beyond the scope of this chapter. In patients with pituitary damage leading to hypogonadism, therapy with gonadotropins can be utilized to induce fertility [34]. Pulsatile gonadotropin-releasing hormone therapy may be ineffective in this patient population if they lack sufficient functioning gonadotrophs. Therapy with other sex steroids (testosterone, estradiol) should be halted while on gonadotropin therapy. As induction of fertility may take months, patients desiring fertility should be referred quickly to fertility specialists to establish care

GH deficiency is common in patients with pituitary adenomas, and replacement therapy with GH, while not essential for life, improves body composition, exercise capacity, bone density, quality of life, and some surrogate markers for cardiovascular risk [13]. Other than a minor worsening in insulin resistance, GH therapy in adults is well tolerated, and observational data to date indicates no increased risk of recurrence of pituitary tumors or increased risk of other malignancies directly attributable to GH therapy [35, 36]. However, due to the theoretical risk, active malignancy is a contraindication to treatment [13]. The concomitant use of oral estrogens will decrease hepatic synthesis of IGF-1, and a higher dose of GH will be needed to achieve a target IGF-1 ([37]); this may become relevant if a patient on GH therapy is started on oral contraceptive pills. Once on a stable dosing regimen, the patient is usually evaluated every 6–12 months (mo). No rigorous data exists to demonstrate a mortality benefit to GH therapy, and GH replacement therapy remains controversial given that treatment is expensive and morbidity benefits are usually small; hence the decision to pursue GH therapy should be individualized, and consideration can be given to stopping the therapy in patients who have no documented improvement after 1 year of therapy.

Treatment of central diabetes insipidus is relatively straightforward and involves replacement with desmopressin, a synthetic analog of ADH, with the goal to control urine output such that it does not adversely affect quality of life. In the outpatient setting, desmopressin is usually given orally or intranasally; duration of effect can be variable, and some patients may require only daily dosing while others may require

TID dosing. Patients are instructed to drink only when thirsty to avoid iatrogenic hyponatremia; it is the author's preference to allow a short window of time every day where the effect of desmopressin has worn off to allow for the clearance of any free water that has accumulated. Management of diabetes insipidus in hospitalized patients with altered mentation or who will be receiving large amounts of intravenous fluids (e.g., perioperatively) requires close monitoring of fluid balance under the care of an endocrinologist or nephrologist.

Finally, it should be noted that some recovery of pituitary function can occur following transsphenoidal resection of a pituitary adenoma [38]. As such, the author typically does not replace nonessential hormones (reproductive hormones, growth hormone) in a patient where surgery is being pursued. Rather the patient is reevaluated 2–3 mo postoperatively with a consideration of hormone replacement if GHD or hypogonadism is persistent. Thyroid hormone and cortisol deficiencies are always replaced preoperatively to lessen perioperative morbidity. The author will often perform reassessment of the need for glucocorticoid therapy postoperatively by having the patient hold their hydrocortisone for 24–48 h prior to their clinic visit at which time an AM cortisol is checked as a rudimentary assessment of hypothalamic-pituitary-adrenal axis integrity [14].

Functional Pituitary Tumors: Background and Diagnosis

Medical therapy often plays an important role in the management of patients with functional pituitary tumors (prolactinoma, acromegaly, Cushing's disease). An overview of the management of pituitary tumors is presented in Table 21.3. An in-depth discussion of the diagnostic evaluation of functional pituitary tumors is beyond the

Table 21.3 Pituitary adenoma management overview

Condition	Usual primary therapy	Additional therapy
Prolactinoma	Medical therapy with DA agonist (e.g., cabergoline)	TSR for nonresponsive tumors if bothersome signs/symptoms from hyperprolactinemia or mass effect Consider radiation to halt growth if large/invasive tumor
Cushing's disease	TSR	Repeat TSR (esp. if first resection incomplete and MRI evidence of residual tumor) Medical therapy (see text) and/or radiation Bilateral adrenalectomy for severe or refractory cases
Acromegaly	TSR	Medical therapy (see text) and/or radiation Screening for and management of comorbidities (e.g., colonoscopy, sleep study)
TSH-oma	TSR	Medical therapy (SRL) and/or radiation; may need additional transient therapy perioperatively (β-blocker, thionamide)
Nonfunctioning adenoma	TSR	Radiation

Abbreviations: *DA* dopamine, *TSR* transsphenoidal resection, *SRL* somatostatin receptor ligand

scope of this chapter. Briefly, prolactinoma is suspected in situations of prolactin excess where the degree of prolactin elevation is proportional to the size of the tumor. Numerous medications cause hyperprolactinemia, and a patient's medication list should be carefully reviewed. Potential diagnostic pitfalls include the "hook effect" (artifactual lowering of prolactin in some immunoassays when high levels are present; this can be unmasked by diluting samples) and stalk effect (mild elevation in prolactin, usually <100) from stalk compression [39]. Prolactinomas >1 cm typically have prolactin levels >250 [9]. The diagnosis of acromegaly involves demonstrating an elevated IGF-1 in conjunction with failure to suppress GH secretion following an oral glucose load [40]. Diagnosis of Cushing's disease is complex and requires at least two unequivocally positive screening tests (24 h urinary free cortisol (UFC), 1 mg dexamethasone suppression test, or late-night salivary cortisol) in conjunction with a nonsuppressed ACTH. In cases where pituitary imaging is equivocal, additional testing (e.g., inferior petrosal sinus sampling, high-dose dexamethasone suppression test) can be considered to differentiate between CD and ectopic ACTH syndrome [41].

Prolactinoma

Prolactinomas represent the most common secretory pituitary tumor [9]. Elevated prolactin levels suppress gonadotropin release resulting in hypogonadism. Given that prolactin is tonically inhibited by hypothalamic dopamine, any type of sellar lesion or pathologic process that compromises flow of dopamine down the pituitary stalk can result in hyperprolactinemia. Pharmacologic dopamine receptor agonists will decrease hyperprolactinemia of any cause; however, their therapeutic use in controlling tumor growth/activity is primarily limited to prolactinoma with additional modest effects in acromegaly [42] and Cushing's disease [43, 44] as discussed in later sections.

Treatment of prolactinoma should be considered for macroprolactinomas (prolactinomas >1 cm), microprolactinomas (prolactinomas <1 cm) with symptoms (e.g., bothersome galactorrhea or hypogonadism in young patients), and microprolactinomas which are enlarging over time [45]. Medical therapy with a DA agonist represents first-line treatment for prolactinoma, even in the case of visual field compromise as rapid improvement in visual field testing can occur with treatment [46]. Cabergoline is the preferred DA agonist due to superior efficacy and tolerability compared to bromocriptine. Common side effects include nausea, orthostasis, and sinus congestion; these can be minimized via gradual dose escalation and administration with food at bedtime. Usual doses are between 0.5 and 2 mg/week (wk). In a large retrospective study, cabergoline normalized prolactin in 92% of patients with microprolactinomas and 77% with macroprolactinomas [47]; additional prospective studies have demonstrated near 100% efficacy if escalating large doses are employed [48]. While cabergoline treatment in Parkinson's disease (where much higher daily and cumulative doses are utilized) is associated with cardiac valvulopathy, the aggregate of data in pituitary patients suggests that cabergoline treatment is not

associated with clinically significant valvulopathy [49]. Regardless, in patients receiving prolonged courses of large cabergoline doses (e.g., >2 mg/wk), close clinical monitoring is suggested, with as needed echocardiography if clinical features suggesting valvulopathy develop.

A small subset of prolactinomas present with or subsequently develop resistance to DA agonists, likely as a result of decreased DA receptor number and impaired downstream signaling [6]. Surgery is an attractive option with resistant microprolactinomas which need treatment as it may be curative. With macroprolactinomas or invasive tumors, surgery and/or radiation can be considered although these modalities are rarely effective in controlling hyperprolactinemia [50]. Options for additional medical therapy to halt growth of invasive tumors are limited; the best studied and most effective is likely temozolomide, which demonstrated efficacy in 15 out of 20 patients treated in the literature [51].

Medical Therapy for Cushing's Disease

Introduction

The decisions to pursue medical therapy for CD and the subsequent choice of agent(s) are complex issues and must be tailored to each individual patient. While transsphenoidal resection (TSR) is the preferred first-line therapy in almost all cases, incomplete resection and/or recurrences are not infrequent, especially with large tumors or if performed by less experienced neurosurgeons [52]. Additional therapy is needed in these cases to prevent long-term morbidity from uncontrolled hypercortisolism; options include repeat resection, radiation therapy, or medical therapy. Even if radiation is pursued, medical therapy is often required as a "bridging" or temporizing measure to control hypercortisolism until the full effect of radiation occurs (usually on the order of months to years) [53].

Medical therapy for CD can be classified based on the physiologic target, with three main classes of agents currently in use. The first class includes pituitary-directed therapies (cabergoline and pasireotide), the second class consists of steroidogenesis inhibitors (ketoconazole, metyrapone, etomidate, and mitotane), and the third class consists of mifepristone, a glucocorticoid receptor antagonist. Small studies have also demonstrated efficacy when agents from different classes are combined [54]. Table 21.4 lists the various agents for the treatment of CD; a discussion of the different classes/agents follows.

Steroidogenesis Inhibitors: General Principles

Steroidogenesis inhibitors decrease cortisol levels via inhibition of adrenal enzymes important for cortisol biosynthesis. ACTH levels often rise as a consequence of decreased cortisol levels and can drive the accumulation of precursors with

Table 21.4 Medical therapy of Cushing's disease

Drug	Dosing	Adverse effects[a]	Clinical considerations
Etomidate (IV)	0.03 mg/kg bolus then 0.05 mg/kg/h with titration to goal (partial or complete blockade) based on (cortisol)	Infusion reactions (thrombophlebitis)	ICU and close monitoring required Allows rapid control in patient unable to take PO medications
Ketoconazole	200–600 mg BID (titrate q2–4wks depending on 24 h UFC values)	↑LFTs, GI upset, drug-drug interactions	Requires close monitoring of LFTs
Metyrapone	0.5–6 g/d (divided TID-QID)	GI upset, ↑adrenal androgen production	Use LC/MS for cortisol measurement (upstream metabolites cross-react with immunoassays)
Mitotane	Up to 3 g/d (divided QID); usually given as block-and-replace strategy	GI upset, neurologic symptoms (lethargy, somnolence)	One third of patients unable to tolerate due to side effects; slow efficacy onset (months)
Cabergoline	1–3.5 mg/wk	Sedation, orthostasis, nausea (well tolerated overall)	Possible escape phenomenon
Pasireotide (SC)	600–900 mg BID	Hyperglycemia, GI upset	Can identify responders early; most useful in pts. with mild elevation in UFC (<2-fold elevated)
Mifepristone	300–1200 mg/d	Hypokalemia, endometrial thickening	Cannot use biochemical assessment of cortisol to titrate dose

Abbreviations: *ICU* intensive care unit, *UFC* urinary free cortisol, *LFT* liver function test, *GI* gastrointestinal, *LC/MS* liquid chromatography/mass spectrophotometry

[a]All therapies have the potential for causing significant adrenal insufficiency (and its associated symptoms)

mineralocorticoid activity or adrenal androgens. Available steroidogenesis inhibitors include ketoconazole, metyrapone, and mitotane; in addition, intravenous etomidate is occasionally used in certain clinical settings. Two treatment strategies exist when using steroidogenesis inhibitors: (1) partial blockade of cortisol synthesis, titrated to a physiologic level of cortisol production, and (2) complete blockade of cortisol synthesis (rendering the patient adrenally insufficient) combined with replacement therapy with physiologic doses of exogenous glucocorticoids ("block-and-replace" strategy). As expected, higher doses of therapy are required during a block-and-replace approach. As noted above, patients with CD treated with steroidogenesis inhibitors often have compensatory increases in ACTH secretion, which may necessitate higher treatment doses than those required in Cushing's syndrome caused by adrenal adenomas or ectopic ACTH-producing tumors (where compensatory increases in ACTH secretion do not occur) .

Ketoconazole

The antifungal ketoconazole decreases cortisol production by blocking several enzymes important for steroid biosynthesis: 11-β-hydroxylase, 17,20-lyase, and the enzyme responsible for cholesterol side chain cleavage. In the largest study to date (retrospective, $n = 200$), ketoconazole normalized UFC in approximately 50% of patients (median dose 600 mg/d); 75% of treated patients had a decrease in UFC by at least 50% [55]. Clinical parameters such as blood pressure and glycemic control improved on therapy. The most common side effects included elevation in liver enzymes (15.8%) and gastrointestinal complaints (13.1%); 2.5% of patients had an increase in liver enzymes more than five times the upper limit of normal (ULN). Ketoconazole has been associated with severe hepatic dyscrasia at an estimated incidence of 1:15,000 ([56]). Elevation in hepatic enzymes from ketoconazole is not related to the dose per se but tends to occur within several weeks after the initiation of therapy or a dose increase. As such, hepatic enzymes are obtained prior to starting therapy and then weekly for the first month with subsequent monitoring occurring less often if doses remain unchanged. Similarly, dose increases require a temporary increase in the frequency of monitoring. Elevation of liver enzymes to more than three times ULN should prompt either dose decrease or cessation of therapy, depending on the degree of elevation. Although ketoconazole carries a black box warning for hepatic toxicity in the United States, the author feels that ketoconazole represents a reasonable medical therapy as long as careful monitoring for toxicity is performed. The clinician should be also aware of the potential for drug-drug interactions given that ketoconazole inhibits cytochrome P450.

Metyrapone

Metyrapone inhibits 11-beta-hydroxylase resulting in decreased synthesis of cortisol and aldosterone; decreased synthesis of aldosterone is not clinically significant due to accumulation of metabolites with mineralocorticoid activity (e.g., deoxycorticosterone) [57]. The largest study to date involved a retrospective analysis of 195 patients with Cushing's syndrome (59% with CD) treated with metyrapone for a mean of 8mo [58]. Of the patients treated with metyrapone monotherapy, 43% had normalization of 24 h UFC and 46% achieved a 09:00 AM cortisol of <12 μg/dL. Adverse effects were primarily gastrointestinal upset (23%, minimized if taken with food) and symptoms of adrenal insufficiency (7%); potassium levels did not decrease, although it is unclear whether patients were treated with potassium supplementation following the initiation of therapy. Hirsutism was not reported, and there was only one case of worsening acne. Frequent monitoring for adverse effects (adrenal insufficiency, hypokalemia) and biochemical efficacy (e.g., 24 h UFC) is required when initiating or titrating therapy. Of note, metyrapone has been used in pregnancy in a small number of cases of Cushing's syndrome without obvious fetal harm [59, 60].

Mitotane

Mitotane inhibits 11-β-hydroxylase, blocks cholesterol side chain cleavage, and has a direct adrenolytic effect. In the largest retrospective analysis to date [61] ($n = 67$ patients), mitotane normalized UFC in 72% of patients with CD after a median of 6.7 mo of treatment. Onset of biochemical control is somewhat delayed compared to other therapies given the lipophilic nature of mitotane and its large volume of distribution. Of note, 28% of patients had to discontinue therapy due to side effects (predominantly gastrointestinal and neurologic). Serum levels of the drug should be monitored as 24 h UFC levels correlate with serum drug levels; in the aforementioned study, a serum mitotane level of >8.5 mg/L was correlated with a normal UFC. Mitotane is usually given in a block-and-replace strategy, and hydrocortisone replacement (at higher than normal doses due to mitotane-induced accelerated clearance) should be started 2–3 weeks after initiating mitotane; mineralocorticoid replacement may not be required in all cases. Assessment for efficacy should occur via monitoring of free cortisol (e.g., 24 h UFC or LNSC) as mitotane increases cortisol-binding globulin [62]. Approximately one third of patients at risk for recurrence can maintain remission >12 mo after the discontinuation of mitotane, presumably from the adrenolytic effect of mitotane. Pituitary tumor growth occurs in 25% of patients on mitotane therapy [61]; hence, judicious MRI surveillance should be considered. Mitotane is teratogenic and should be avoided during pregnancy.

Etomidate

Etomidate is an intravenous hypnotic which also inhibits 11-β-hydroxylase and cholesterol side chain cleavage, resulting in decreased cortisol biosynthesis. Studies examining the treatment of Cushing's syndrome with etomidate are limited and primarily consist of case reports and small series (reviewed in [63]). Infusion of etomidate results in rapid control of hypercortisolemia within 12 h; doses required to achieve control of cortisol secretion do not typically induce sedation and cortisol levels rise to baseline 24 h after the discontinuation of etomidate (drug half-life =3–5 h) [64]. Therapy should be administered in an intensive care unit setting via a central line (due to the propylene glycol vehicle which can cause thrombophlebitis); careful monitoring of adverse effects (sedation, potassium disturbances) and clinical response (e.g., serial monitoring of serum cortisol levels q4h) is required. Doses should be decreased in elderly patients or those with renal insufficiency. Etomidate is particularly useful in acutely ill patients unable to take oral therapy, e.g., patients with Cushing's-induced psychosis and in severely hypercortisolemic patients prior to emergent bilateral adrenalectomy.

Cabergoline

Given the expression of DA receptors on corticotroph adenomas [65], a limited number of studies have examined the role of cabergoline treatment for CD, typically in the setting of persistent/recurrent disease after TSR. The largest prospective study

to date ($n = 20$ patients) demonstrated normalization of 24 h UFC in 75% of patients at 3mo; however, this decreased to 40% after 24 months of therapy (median dose =3.5 mg/wk) indicating escape from the therapeutic effect of cabergoline in a significant number of patients [43]. Response to treatment was not correlated with hyperprolactinemia. The largest retrospective study to date ($n = 30$ patients) demonstrated normalization of 24 h UFC in 30% of patients at a mean follow-up of 37mo (median dose 2.1 mg/wk) [44]. In general, therapy was well tolerated and safe; one patient had documented progression from mild to moderate tricuspid regurgitation. While the side effect profile and lack of drug-drug interactions make cabergoline an attractive option, efficacy data is limited, and there appears to be a significant potential for escape from the therapeutic effect over time.

Pasireotide

Pasireotide is an SST5 receptor agonist approved since 2012 for the treatment of CD. The largest clinical trial to date involving pasireotide consisted of 162 CD patients treated for 12mo with a primary endpoint of normalization of UFC at 6mo [66]. At a dose of 900 μg sc BID, pasireotide normalized UFC in 26% of patients and was associated with a 44% decrease in mean tumor volume. The vast majority of responders could be identified within 2mo of treatment, and mean UFC levels decreased by approximately 50%. Additional analysis indicates improvements in signs and symptoms of hypercortisolism (blood pressure, lipid profiles, weight, quality of life) at 12mo [67]. The most notable side effect was hyperglycemia (likely mediated by decreased incretin secretion ([68])); a new diagnosis of type 2 diabetes was made in 48% of patients (mean A1c increase of 1.6%), and the initiation of an additional antidiabetic therapy was required in 64% of patients. Other notable effects include gastrointestinal symptoms (similar to other somatostatin analogs), cholelithiasis (30%), elevation in liver enzymes (10%), QT prolongation (<2%), and presumed suppression of GH/IGF-1 based on the known pharmacology of somatostatin receptor agonists.

A trial of pasireotide (usual dose, 900 μg SC BID) can be considered in patients with mild elevations in UFC (less than two times ULN). In patients with significant elevations of UFC or with minimal response after 2mo of treatment, the utility of continued therapy is questionable and the adverse effects (significant hyperglycemia and development of diabetes) likely outweigh the benefit. Pasireotide would also be an unattractive option in a patient with uncontrolled diabetes. Current guidelines suggest obtaining baseline liver function tests, IGF-1, fasting glucose, A1c, thyroid studies, gallbladder ultrasonography, and an ECG prior to initiating treatment [69]. Repeat monitoring of these parameters is suggested 3mo after dose initiation or change. Close monitoring of blood glucoses at home is warranted given the potential for hyperglycemia.

Glucocorticoid Receptor Antagonists (Mifepristone)

Mifepristone is a progesterone receptor antagonist historically used for inducing abortion; at higher doses, it also blocks the glucocorticoid receptor. A prospective trial of 50 patients with hyperglycemia and/or hypertension (HTN) due to Cushing's syndrome (majority with CD) demonstrated improvement in clinical parameters following 6mo of therapy [70]. A1c decreased by a mean of 1.1%, weight decreased by a mean of 5.7 kg, 38% of patients had improvement in diastolic blood pressure of >5 mm Hg, and quality of life scores significantly improved. Notable side effects included antiprogestin effects (endometrial thickening, 20%), increased mineralocorticoid activity (hypokalemia, 65%), and symptoms suggestive of adrenal insufficiency (nausea/fatigue, 48%). In a long-term extension, 11% of patients with CD treated for a median of 11.3mo (some of whom had prior radiation therapy) had documented tumor growth [71]. ACTH and cortisol levels rise significantly on therapy, making biochemical monitoring for efficacy challenging. In general, dosing should begin with the lowest dose with gradual uptitration based on clinical parameters. Close monitoring of clinical response (e.g., weight, glucose control) and potassium is mandatory; periodic monitoring of endometrial thickness (e.g., yearly transvaginal US) and pituitary tumor size is also prudent, particularly in patients with macroadenomas. In addition to improving glucose control in hyperglycemic Cushing's patients, others have suggested additional uses for mifepristone in acute control of severe hypercortisolemia [54]. Mifepristone-induced adrenal insufficiency can be treated with dexamethasone; 1 mg dexamethasone usually overcomes the effect of 400 mg mifepristone [72].

Combination Therapy

Inhibiting pituitary tumor-driven hypercortisolism at different target sites makes physiologic sense; however, data are limited. Several combinations of medical therapies have been employed. A small prospective study (n = 14 patients) demonstrated improved biochemical control with a combination of ketoconazole and cabergoline compared to monotherapy [73]. A sequential escalating regimen of pasireotide followed by addition of cabergoline then ketoconazole resulted in biochemical normalization in 15 of 17 patients with Cushing's disease [74]. A regimen of ketoconazole, metyrapone, and mitotane normalized hypercortisolism within 48 h in 11 patients with severe Cushing's syndrome [2], suggesting that it may be a medical alternative to emergent bilateral adrenalectomy. While more studies are needed, combination therapy should be considered in patients refractory to medical monotherapies.

Medical Therapy of Acromegaly

Medical control of the detrimental effects of excess GH is achieved through agents that decrease GH secretion from the pituitary (e.g., DA agonists or somatostatin receptor ligands [SRLs]) or via direct antagonism of the GH receptor (e.g., pegvisomant).

Table 21.5 Medical therapy of acromegaly

Drug	Dosing	Adverse effects	Clinical considerations
Cabergoline	1–3.5 mg/wk. (titrate q4–6 wks)	Sedation, orthostasis, nausea (well tolerated overall)	Most effective in cases of mild GH excess (e.g., IGF-1 < 150% ULN)
Octreotide LAR (IM)	20–40 mg monthly	GI cramps and diarrhea (both usually resolve over time), ↑risk of gallstone disease	Must be reconstituted
Lanreotide ATG (deep SC)	60–90 mg monthly	Same as above	Comes in prefilled syringes
Pasireotide LAR (IM)	20–60 mg monthly	Hyperglycemia; otherwise similar to other SRLs	May have higher efficacy than other SRLs; caution if preexisting DM2
Pegvisomant (SC)	10–30 mg daily	Injection-site reactions, ↑LFTs	Theoretical risk of tumor growth; has beneficial effect on glycemic control

Abbreviations: *GI* gastrointestinal, *HA* headache, *ULN* upper limit of normal, *IM* intramuscular, *SC* subcutaneous, *SRL* somatostatin receptor ligand, *DM2* diabetes mellitus type 2, *LFT* liver function tests

An overview of pharmacologic agents for acromegaly is presented in Table 21.5. Combination therapy with agents from both classes also represents a viable option in refractory cases [75]. Similar to CD, medical therapy in acromegaly is utilized postoperatively if persistent or recurrent disease is present, while awaiting the therapeutic effects of radiation to occur, or as primary therapy in a nonoperative patient. Biochemical targets for treatment include a normal IGF-1 (for age/sex) and a random GH <1 μg/L [40]. The clinician should remember that medical management of a patient with acromegaly extends beyond simply controlling GH hypersecretion – the clinical sequelae of prolonged GH hypersecretion should also be directly addressed. Published suggestions include colonoscopy at diagnosis (followed by every 5–10 year depending on the control of GH secretion), assessment for/treatment of sleep apnea, evaluation of nodular thyroid disease if present, and aggressive management of metabolic comorbidities (diabetes, HTN, hyperlipidemia) [40].

Cabergoline Therapy in Acromegaly

In a meta-analysis of 150 acromegalic patients, cabergoline (mean dose 2.6 mg/wk) demonstrated 34% efficacy in normalizing IGF-1 levels; there was no statistically significant relation between the baseline prolactin concentration and the degree of change in IGF-1 levels [42]. The largest single prospective study to date (n = 64 patients) demonstrated improved efficacy of cabergoline when baseline IGF-1 levels were only mildly elevated (53% efficacy) compared to when baseline IGF-1 levels were significantly elevated (17% efficacy) [76]; hence, cabergoline is a less attractive option in cases of higher GH secretion rates (e.g., IGF-1 > 150% ULN). Advantages of cabergoline therapy compared to other acromegaly therapies

include an oral route and reduced cost. The same concerns regarding valvulopathy exist when using cabergoline to treat acromegaly; however, studies to date have not demonstrated significant valvulopathy in acromegalic patients on long-term cabergoline therapy [77].

Pegvisomant

Pegvisomant, a GH receptor antagonist, blocks the peripheral effects of GH and leads to normalization of IGF-1 levels in up to 97% of acromegalic patients in a clinical trial environment where close monitoring and aggressive dose titration are pursued [78]. A surveillance study of 1288 patients treated with pegvisomant demonstrated a lower overall efficacy of 63%, presumably reflecting inadequate dose titration or patient noncompliance [79]. GH levels rise on pegvisomant and cannot be used as an indicator of biochemical control. While some patients (~17%) developed antibodies against pegvisomant, tachyphylaxis was not seen in a large study of patients ($n = 160$) followed up for a mean of 425 days [78]. A theoretical risk of tumor growth exists with pegvisomant as it does not act at the level of the pituitary; up to 6.7% of patients demonstrate tumor growth while on therapy [80], and MRI at baseline, 6mo after initiation, 1 year after initiation, and then yearly thereafter has been suggested [40]. About 2.5% of patients develop significant elevations of transaminases; liver function tests should be monitored monthly for 6mo followed by q6mo monitoring thereafter, with discontinuation of therapy if levels rise more than three times ULN. Advantages of pegvisomant include higher efficacy than other therapies (assuming adequate dose titration); downsides include cost and administration (daily subcutaneous injection in most cases) .

Somatostatin Receptor Ligands

Several formulations of somatostatin receptor ligands (SRLs) are currently approved for the treatment of acromegaly and include short-acting formulations (octreotide) and long-acting depot formulations (octreotide LAR, lanreotide autogel, pasireotide LAR). Most patients treated with SRLs use depot formulations due to dosing convenience. Due to long half-life, dose titrations should occur after a minimum of 3mo on a particular dose with biochemical assessment for efficacy performed immediately prior to receiving a dose.

Octreotide LAR and lanreotide ATG represent the primary depot SRLs in current widespread use. While clinical experience with these compounds is extensive, their true efficacy remains somewhat uncertain given heterogeneity in past studies and changes in the biochemical assessment of remission over time. Previous studies suggested an efficacy of 50–70% [81], although recent studies in patients not prescreened for SRL responsiveness and in whom the agents were used as primary therapy demonstrated significantly lower response rates (~20–30%) [82–84]. Octreotide LAR and lanreotide ATG appear equally efficacious [85]. Tumor shrinkage

occurs in up to 66% of patients treated with SRLs; 59% of patients experience tumor shrinkage of >50% [86]. Dosing intervals can be increased (e.g., to every 6–8 weeks) in patients well controlled on long-acting SRLs [86].

Pasireotide LAR binds both SSTR 2 and 5, resulting in a theoretical advantage over conventional SRLs, which primarily bind SSTR 2 ([87]). A head-to-head comparison of pasireotide LAR vs. octreotide LAR in 358 acromegalic patients treated for 1 year demonstrated improved efficacy (defined as normal IGF-1 with GH <2.56 μg/L) with pasireotide LAR compared to octreotide LAR (31% vs. 19%) [84]. The lower-than-expected efficacy of octreotide LAR in this study may reflect inadequate dose titration. As expected, hyperglycemia was a significant adverse effect with pasireotide LAR (rise in A1c of 0.9% in patients with preexisting diabetes treated with pasireotide LAR); this effect is not typically seen with other SRLs [88].

As of 2015, an oral form of octreotide was currently under US government review for the treatment of acromegaly. In a study of 155 acromegalic patients responsive to injectable SRLs, an oral formulation of octreotide maintained a comparable level of biochemical control in 62% of patients after 1 year [89]. Oral octreotide may represent a future option for patients already reasonably controlled on an injectable SRL who desire an oral formulation; of note, dosing is BID and must occur >1 h before and at least >2 h after a meal to avoid absorption interference from food.

Combination Medical Therapy in Acromegaly

A substantial proportion of acromegalic patients remain uncontrolled on medical monotherapy. Studies have examined the role of combining SRLs with cabergoline, combining SRLs with pegvisomant, or combining pegvisomant with cabergoline. A meta-analysis of 77 patients with inadequate control on SRLs demonstrated that addition of cabergoline (mean dose 2.5 mg/wk) resulted in normalization of IGF-1 in 52% of those treated with combination therapy; the baseline prolactin concentration was not predictive of response [42]. Addition of pegvisomant to patients inadequately controlled on SRL monotherapy results in efficacy rates of 95% [90], although the efficacy of combination therapy is likely similar to pegvisomant monotherapy [91]. Addition of pegvisomant to patients already controlled on SRL monotherapy may improve quality of life [92]. Combining pegvisomant with an SRL decreases the dosing requirements for each drug [90, 93, 94], which may improve patient convenience and compliance. A prospective study of 24 patients treated with cabergoline (0.5 mg/daily) demonstrated increased efficacy when low-dose pegvisomant (10 mg/d) was added (increase from 17% to 68%); subsequent withdrawal of cabergoline decreased efficacy to 26% [95]. The aggregate of data suggests that various combinations of SRL, pegvisomant, and cabergoline may increase biochemical efficacy, improve quality of life, and decrease dosing requirements while maintaining a similar side effect profile compared to monotherapy.

TSH-Secreting Pituitary Adenoma

TSH-secreting pituitary tumors (TSH-omas) represent <1% of pituitary tumors [96] but are often clinically significant due to resulting hyperthyroidism. Cosecretion of GH and prolactin has been observed [97] and can result in characteristic symptoms of GH or prolactin excess. Biochemical abnormalities in TSH-oma mimic those seen in the syndrome resistance to thyroid hormone (RTH); TSH-oma is suggested by an elevated alpha subunit (and elevated alpha subunit/TSH molar ratio), an elevated sex-hormone-binding globulin, and the presence of an adenoma on MRI [98]. While TSR is the preferred treatment, it is often not curative in macroadenomas given the fibrous and invasive nature of TSH-omas [98]. Achievement of euthyroidism preoperatively is required to minimize morbidity; SRLs in usual doses (e.g., octreotide LAR 20–40 mg IM q28d) normalize free T4 levels in >80% of patients [96]. While experience with cabergoline is limited, its efficacy is likely substantially less than SRLs [96]. In patients with persistent hyperthyroidism despite SRL therapy, additional treatment with thionamides and/or beta-blockers can be initiated to minimize the manifestations of hyperthyroidism. Treatment of residual disease to prevent the sequelae of long-term hyperthyroidism is required; medical therapy with SRLs and/or radiation therapy are often employed in the postoperative setting. Patients on medical therapy are typically followed up closely with free T4 levels (e.g., q6–12wks) until euthyroidism on a constant dose of SRL is achieved; clinical and biochemical monitoring can then decrease to q6–12mo.

Conclusion

Medical management of pituitary adenoma patients is a complex endeavor that requires an understanding of pituitary physiology, an awareness of the clinical consequences of pituitary hormone deficiency and excess, and knowledge of the various treatment options available for patients with pituitary disease. Appropriate recognition and treatment of hypopituitarism is critical in the preoperative/perioperative setting and is important for minimizing long-term morbidity. Medical treatment of patients with functional pituitary tumors can either serve as primary therapy (e.g., prolactinoma) or as a secondary therapy following surgery and/or radiation (e.g., persistent/recurrent Cushing's disease or acromegaly). In most cases, several options for medical therapy exist, and the efficacy and side effect profile of each agent must be carefully considered before a specific therapy is undertaken. Combination medical therapy can be effective when monotherapy fails. A sound understanding of the medical therapies available for hypopituitarism, prolactinoma, Cushing's disease, and acromegaly will enable a clinician to best care for the complex medical issues that accompany patients with pituitary tumors.

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Transsphenoidal Surgery for Recurrent Pituitary Disease

22

Joshua Bakhsheshian and Gabriel Zada

Introduction

Transsphenoidal surgery (TSS) is the preferred approach for the surgical treatment of pituitary adenomas. It provides direct access to the sella without brain retraction, and remains the most commonly used approach for pituitary adenoma resection. Even in the hands of experienced surgeons, however, recurrent pituitary disease is seen in approximately 20% of the patients. Options for recurrent pituitary adenomas include repeat surgery, stereotactic radiosurgery or external beam therapy, medical treatment for selected functional adenomas, or serial monitoring. Repeat surgery remains a viable option for many recurrent pituitary adenomas, especially in the presence of neurologic deficits due to mass effect on the optic nerve/chiasm and normal pituitary gland. Repeat surgery can be more complicated due to altered anatomical landmarks and scar tissue from prior surgical approaches. The surgical success rates for recurrent disease are often lower than for primary disease, and carry higher rates of complications. Therefore, mature and careful selection of the goals and approaches are critical factors in success when considering repeat transsphenoidal surgery for recurrent pituitary adenomas. In this chapter, we review technical considerations and the data pertaining to surgical outcomes following the transsphenoidal approach for recurrent pituitary disease.

J. Bakhsheshian, MD, MS
Department of Neurological Surgery, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

G. Zada, MD, MS (✉)
Department of Neurological Surgery, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Neuro-Oncology and Endoscopic Pituitary/Skull Base Program, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
e-mail: gzada@usc.edu

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_22

Recurrent Disease

Reported recurrence rates for pituitary adenomas vary between 6 and 27%, with a median time to recurrence of 3–5 years [1–3]. Numerous risk factors have been associated with recurrent disease, including tumor invasiveness and size and the degree of elevation in hormone levels [3–7]. The reported rates of nonfunctioning and functioning pituitary adenoma subtypes are separately discussed below.

Nonfunctioning Pituitary Adenomas Nonfunctioning pituitary adenomas (NFPAs) are often macroadenomas at the time of presentation and frequently demonstrate suprasellar extension or cavernous sinus invasion with mass effect on surrounding neurological structures. The degree of tumor invasion frequently mandates subtotal tumor resection, as shown by Knosp et al. and other authors [3, 8–10]. Therefore, the goals of surgery for invasive macroadenomas are often to achieve maximal safe tumor resection, with an emphasis on decompression of the optic apparatus and preservation or restoration of normal pituitary function. Recurrence of NFPAs is defined as reappearance of tumor on radiological imaging (usually MRI) following total resection, and has been reported to occur in 6–20% of the patients after surgical treatment [5, 8]. Chang et al. retrospectively analyzed 663 patients who had undergone a transsphenoidal approach or transfrontal craniotomy for primary NFPAs during 1975–1995. With a mean follow-up of 8.4 years, 64 (9.7%) recurrences occurred after surgical treatment. The authors found that cavernous sinus invasion was more likely to result in subtotal resection. Dallapiazza et al. retrospectively analyzed 80 patients who underwent endoscopic TSS for nonfunctioning pituitary macroadenomas with greater than five-year postoperative follow-up, and found 7 (12%) recurrences of disease after gross total resection and 14 (28%) patients with progression of disease after subtotal resection [5]. The authors redemonstrated that the Knosp grade, based on the degree of invasion of the cavernous sinus, was associated with recurrent disease.

Cushing's Disease Long-term management of patients with recurrent Cushing's disease after initial successful TSS remains a major challenge. Immediately following the surgical resection of an ACTH-secreting pituitary adenoma, serial cortisol levels are measured until a low baseline cortisol level (optimally <2 μg/dL) is achieved. Remission following surgery is defined by a normal 24-h urine free cortisol level. Similarly, recurrent Cushing's disease is defined as an elevated 24-h urine free cortisol level with clinical symptoms consistent with Cushing's disease, while not receiving glucocorticoid replacement. Several studies have reported a recurrence rate of 5–27% after initial TSS [2]. Yamada et al. retrospectively analyzed 307 patients who underwent pituitary surgery for Cushing's disease and found that peak cortisol levels ≥9.4 μg/dL in response to corticotropin-releasing hormone (CRH) and cavernous sinus invasion were significant predictors of recurrence [6]. The authors also found that tumor recurrence was more common in patients with sparsely granulated adenomas than in those with densely granulated adenomas.

Acromegaly In acromegaly cases, it is important to differentiate between recurrences after biochemical cure and persistent disease after unsuccessful surgery [11]. A cure of acromegaly is defined as a basal growth hormone (GH) level below 2.5 μg/L, suppression of GH to 1 μg/L during an oral glucose tolerance test, and an IGF-1 level that is normal for age and gender [12]. Although recurrence after surgical resection in acromegaly cases is less frequent (0.4–3%) than other pituitary adenomas, persistent disease with GH hypersecretion remains common (43%) [11]. In 506 patients with acromegaly undergoing primary transsphenoidal surgery, Nomikos et al. found the overall rate of remission rate to be 57.3% [4]. During a follow-up period of 10.7 years, only two recurrences (0.4%) occurred. Tumor recurrence was less likely to occur in patients with a low postoperative GH concentration, low glucose-suppressed GH concentration, or normalization of the paradoxical GH increase after TRH infusion [3].

Prolactinoma Although TSS is an effective therapeutic option for most pituitary adenomas, it is not the first line of treatment for prolactinomas. TSS may be indicated in patients with prolactinomas that are resistant or intolerant to pharmacological management, or are experiencing progressive tumor growth despite maximal medical management. It may also be considered in patients who are unable to tolerate dopamine agonist medications for a variety of reasons. Recurrence rates of prolactinomas after surgical resection have varied from 13 to 25% [3, 13]. A systematic review and meta-analysis of factors associated with the recurrence of all pituitary adenomas after surgical remission reported the highest recurrence rate in patients with prolactinomas. Age, gender, and tumor invasion were not found to be significant factors for recurrence, whereas low basal postoperative prolactin and normalization of thyrotropin-releasing hormone levels were favorable clinical factors associated with longstanding remission or cure [3].

Indications for Repeat Surgery

Primary indications for repeat surgery include visual loss, endocrine abnormalities, or imaging evidence of tumor progression or recurrence (Table 22.1) [14]. Adequate preoperative imaging studies are essential because of the wide range of pathologies

Table 22.1 Indications for repeat surgery

Type of adenoma	Common surgical indications
Nonfunctioning pituitary adenoma	Headache, visual deficits, hypopituitarism, apoplexy
GH adenoma	Rapid relief of endocrinopathy, mass effect, failure of medical therapy, apoplexy
ACTH adenoma	Prompt relief of endocrinopathy, apoplexy
PRL adenoma	Failure of medical therapy, apoplexy

ACTH adrenocorticotropic hormone, *GH* growth hormone, *PRL* Prolactin

that can be found in the sellar region. In functioning adenomas, it is important to have identified an anatomic target for resection, except for patients with Cushing's disease who often have negative imaging. TSS can safely be utilized to resect the majority of recurrent pituitary adenomas. Most adenomas have a soft consistency and can be safely removed with curettage and suction during TSS. However, if the tumor demonstrates significant suprasellar extension, lateral extension, retrosellar extension, brain invasion with edema, firm consistency, and/or involvement of vascular or optic structures, an open craniotomy may be preferred to maximize patient safety [15].

There are few contraindications for TSS that should be addressed preoperatively. Endocrine dysfunction from Cushing's disease, secondary hyperthyroidism, or panhypopituitarism should be optimized prior to surgery. Active sinusitis should be treated with antibiotics prior to surgery to decrease the risk of meningitis. Ultimately, the decision to treat the patient with TSS for recurrent disease should be made on an individualized basis.

Preoperative Management

After the patient is selected as a surgical candidate, a comprehensive preoperative evaluation is conducted to minimize the risks for potential complications. Checklists can be used to avoid potential preoperative or intraoperative complications (Tables 22.2, 22.3 and 22.4) [16, 17]. Preoperative endocrine analysis is essential, and adequate stress doses of steroids should be administered when indicated. We typically reserve administration of corticosteroids for patients who demonstrate adrenal insufficiency on preoperative testing, keeping in mind that hypopituitarism is more common in patients with prior transsphenoidal surgery and recurrent pituitary adenomas. A complete ophthalmologic evaluation is also recommended for all patients with visual complaints, especially in patients who have tumors with suprasellar extension. Having a preoperative ophthalmologic exam also allows the surgeon to track progressive changes with serial exams.

A preoperative MRI should be acquired to further characterize the tumor and its extension pattern [18]. The acquisition of CT imaging with fine slices can help delineate distortions or anomalies in the bony structures of the nasal approach, sinuses, and sellar anatomy. It is important to note the side-to-side working distance between the carotid arteries and in relation to the tumor and optic nerves. The number and orientation of the septa in the sphenoid sinus can help orient the surgeon intraoperatively. Preoperative CT and MR imaging can also be integrated for intraoperative navigation. Any concern about iatrogenic vascular trauma from the primary surgery must also be addressed. Therefore, MR, CT, or conventional angiography may be indicated in a minority of cases.

Postoperative CSF leaks are always of concern, and the risk of intraoperative and postoperative CSF leaks are higher in repeat surgery. Therefore, preoperative placement of a lumbar drain may be used at the surgeon's discretion to decrease the risk of a CSF leak and facilitate its repair [19]. An otolaryngologist can assess the extent of scar tissue and anatomical distortions in the nasal pathway with nasal endoscopy,

Table 22.2 Preoperative checklist for endoscopic endonasal surgery

Category	Item	Subitem
History and Physical exam		
Laboratory tests	General labs	CBC, BMP, PT/PTT, INR, type and screen
	Hormonal labs	PRL, a.m. cortisol, ACTH, TSH, free T4, FSH, LH,
		free testosterone, GH, IGF-I
	Stimulation testing (as needed)	
	PRL level dilutions (as needed to rule out hook effect)	
Imaging	MRI of sella w/ or w/o contrast; sagittal and coronal sequences	
	CT (as needed)	
	MRA or CTA (as needed to rule out vascular lesion)	
	MRI or CT for neuronavigation	
Informed consent	Procedure	Fat/fascial graft, lumbar drain
	Tumor bank/clinical trial	
Meds	Corticosteroid, thyroid replacement therapy	Hydrocortisone, levothyroxine
	Discontinue blood thinners	
Consultations	Endocrinology	
	Ophthalmology (visual field testing)	
	Medical clearance	

From Christian et al. [16]
CTA CT angiography, *INR* international normalized ratio, *Meds* medications, *MRA* MR angiography

and this can provide more information to guide the decision about the type of approach to employ. Development of a pedicled, nasal-septal flap can often still be performed in repeat operations, especially if the prior approach was a unilateral endonasal or sublabial approach. A multidisciplinary team consisting of a skull-base neurosurgeon, otolaryngologist, endocrinologist, and ophthalmologist should be formed for optimal outcomes and to streamline surgical planning.

Intraoperative Preparation and Positioning

Perioperative antibiotics are routinely given 1 h before surgery to ensure therapeutic blood levels. Prior to induction of anesthesia, the surgeon and anesthesiologist should review the case and discuss potential complications. General anesthesia is then performed as usual. Patients with acromegaly may require awake or fiberoptic intubation due to underlying cardiomyopathy, airway edema, and macroglossia [20]. After intubation and induction, the nasal region is disinfected with povidone-iodine and prepared with nasal decongestants. Patties soaked with 0.02% oxymetazoline can be

Table 22.3 Intraoperative checklist for endoscopic endonasal surgery

Category	Item	Subitem
Surgical timeout	Patient ID, procedure, allergies, meds	
Meds	Antibiotics	Ancef, vancomycin
	Corticosteroids	Hydrocortisone, dexamethasone
Imaging	MRI of sella w/ or w/o contrast; sagittal & coronal sequences displayed in OR	
Adjunctive measures	Endotracheal tube positioning	Routine
	Radial arterial line	Routine
	Orogastric tube or oral packing	Routine
	Lumbar drain	Extended approaches
	Foley catheter	Extended approaches
Positioning	Head elevated above thorax	
	Flexion/extension for extended approaches	
Neuronavigation	Registration performed w/good accuracy	
Preparation	Nasal	Oxymetazoline, lidocaine w/ epinephrine, iodine prep
	Abdomen or thigh for fat/fascial harvest	
	Pedicled nasoseptal flap	Extended approaches
Equipment	Endoscopy system	0°, 30°, & 45° telescopes
		Camera
		Light source & fiberoptic cable
		HD monitor
		Clearvision or other lens irrigator
		Recording equipment
	Microscope	As needed for backup
	Sinus debrider	
	Sinus & skull base instruments	
	Micro-Doppler	
	Tumor resection instruments	Nico Myriad, CUSA, SonoPet
	Reconstruction materials	DuraSeal, fibrin glue, Porex plate
Surgical terminus	Removal of throat packs or OGTT suctioning	
	Pupillary/visual check (prior to leaving OR)	

From Christian et al. [16]

placed between the middle turbinates and septum using a nasal speculum and bayonet forceps. They are left in the nasal cavity for 5–10 min.

The patient is then placed in a semirecumbent ("beach chair") position with the back table at 20° angle from the horizontal and the head on a horseshoe (or Mayfield skull clamp if neuronavigation is being used). This allows the head to be above the

Table 22.4 Postoperative checklist for endoscopic endonasal surgery

Category	Item	Subitem
Physical exam	General neurological exam	
	Visual acuity & fields	
Laboratory tests ordered	Sodium levels	Every 6 or 12 h
	Monitoring for DI	If UOP >250 mL/h for 2 consecutive hours, send immediate specific gravity and sodium
	Next-day a.m. labs	CD: cortisol level every 6 h
		Acromegaly: a.m. GH level
		HPA axis monitoring: cortisol level every a.m.
		Prolactinoma: PRL level every a.m.
Imaging	MRI of sella w/ or w/o contrast; sagittal & coronal sequences	Either w/in 72 h or in 3 mos
Special orders	Lumbar drain specifications	
	Set time for removal of nasal packing (if used)	
Meds	Antibiotics	
	Hormone replacement	
	DDAVP	
Discharge planning	Sodium level on postop Day 7	
	Follow-up w/ endocrinologist & ophthalmologist	

From Christian et al. [16]
HPA hypothalamic-pituitary-adrenal, *UOP* urine output

heart, and facilitates venous drainage while decreasing venous pressure within the cavernous sinus. The right shoulder is placed at the upper right-hand corner of the table; the patient's left ear is pointed toward the left shoulder, and the table is turned so that the patient's head remains parallel to the wall of the operating room. This allows the surgeon to stay in close proximity to the surgical field without bending over the patient. The head can be rotated to the right for easier surgical access, while keeping the dorsum of the nose parallel to the floor so that the endonasal trajectory is toward the sella. Note that overflexing the neck can kink the endotracheal tube in the pharynx or obstruct the jugular vein, and this can result in increased bleeding. The monitors used for image guidance and endoscopy can be positioned directly in front of the surgeons.

The patient is then draped in sterile fashion. Given that the sellar floor may be partially or wholly absent, the lateral thigh (or abdomen) should also be prepared to harvest a fascial graft in anticipation of sellar reconstruction and for repair of an intraoperative CSF leak. The nasal mucosa can then be injected with 1% lidocaine with 1:200,000 epinephrine. In endoscopic cases, the middle turbinate and posterior nasal septum are routinely injected. The nasal mucosa can be dissected away from the cartilaginous septum with the injection solution (referred to as hydrodissection) under direct endoscopic visualization.

Transsphenoidal Access

After the decision is made to perform a transsphenoidal approach, the option of using a microscope or an endoscope remains. At a majority of centers, the endoscopic approach has become the preferred operative approach to the sella and parasellar skull base. The endoscope offers panoramic and angled views that allow the surgeon to visualize a greater portion of the tumor, thereby promoting resection under direct visualization [10]. The advantages of the endoscope are most appreciated with larger tumors. However, the surgeon must create a larger exposure for the addition of the endoscope, which can increase the potential for posterior sinonasal complications that require postoperative nasal care. The endoscopic approach can also be converted to a standard microscope approach if there is extensive scarring, bleeding, bony overgrowth, nasal-septal perforation/defects, and nasal/sphenoid polyps from prior surgery, although this is seldom required once sufficient experience is gained in skull-base endoscopy [14, 21]. At our center, we have fully transitioned to an endoscopic endonasal approach utilizing a two-surgeon, four-handed microsurgical methodology for both initial and recurrent TSS cases.

Regardless of the approach used, one must exercise great caution during the exposure. If the dissection or trajectory is carried too anterior, the surgeon may encounter arachnoid folds while risking a CSF leak. If the dissection or trajectory is carried too posterior, the surgeon might find himself or herself exposing dura over the posterior fossa. It is important to keep a midline trajectory, and one should always use standard anatomical landmarks and selective neuronavigation to guide a safe approach. A reliable anatomical midline target in most patients, even in redo operations, is the junction where the vomer (inferiorly) and perpendicular plate of the ethmoid (superiorly) connect with the rostrum of the sphenoid sinus.

Endoscopic Approaches

Endoscopic approaches can vary between one surgeon using the endoscope holder with a two-hand approach, and two surgeons using a three- or four-handed approach. If needed, a unilateral partial middle turbinectomy can be employed to increase the room for instruments, although this is seldom required. The senior author's preference is to have two surgeons performing a bimanual-binarial dissection with one surgeon dedicated to positioning of the endoscope and the other surgeon dedicated to microdissection using two hands.

The majority of the exposure and tumor resection can be completed with a zero-degree endoscope. The endoscope is generally placed within the right nostril, identifying the inferior and middle turbinates. Once the middle turbinate is lateralized, the choana and sphenoethmoid recess can be identified. The sphenoid ostium can then be found posterior to the inferior third of the superior turbinate. The sphenoid cavity can also be located and penetrated by advancing superiorly along the sphenoethmoid recess for approximately 1.5 cm. The posterior portion of the septum is then incised to identify any remnants of the vomer and perpendicular plate of the ethmoid (midline keel) and subsequently the contralateral sphenoid ostium. The

bone between the sphenoid ostium can then be removed with a high-speed diamond burr (5 mm diameter) or Kerrison rongeurs. The contralateral nare can now be entered. The medial turbinate on the left side is generally lateralized in a similar fashion and not resected. A horizontal incision can be made in the nasal mucosa, starting at the sphenoid os and carried to the posterior region of the nasal septum. The mucosa can then be swept superiorly and anteriorly, while allowing the option to harvest a pedicled graft if needed (referred to as the nasoseptal rescue flap) [22]. The posterior septectomy can then be completed, coming as far anterior as the anterior border of the middle turbinate. Care should be taken to avoid injury to the sphenopalatine artery, which can be found at the inferolateral borders of the sphenoidotomy. This artery has two branches that vascularize the nasal septum and nasal wall. In case of intraoperative bleeding, the use of bipolar coagulation is preferred.

Depending on any prior surgical approach(es), certain changes can be made to modify the operation [1]. In cases in which a previous transcranial approach had been performed, the procedure can follow the same steps of a primary endoscopic transsphenoidal approach. The middle turbinates might have been lateralized in both nostrils, or removed unilaterally when an extended approach was performed with a previous microscopic or endoscopic TSS. Additionally, nasal-septal deviations are very common if prior unilateral endonasal approaches have been performed, and should be identified preoperatively. In previous endoscopic TSS, the approach starts with management of nasal synechiae, especially between the nasal septum and the turbinates. In the majority of cases, a wide communication between the nasal and sphenoid cavities should be present, and the sella can be reached with the endoscope without dissecting any structures. Other times, identification of the sphenoid ostia may be more challenging due to the presence of scar tissue. Due to the likelihood of abnormal anatomy, we routinely use neuronavigation for all repeat transsphenoidal operations.

Sphenoid Sinus Exploration

Relative to the microscopic approach, the anterior sphenoidotomy for endoscopic approaches is generally larger, due to the requirement to dock the endoscope and facilitate access for multiple instruments in the operative field while avoiding collisions. To optimize the available working space, the endoscope can be docked superiorly at the 12 o'clock position in the patients' right nare, and dissection tools can be introduced via both nostrils and manipulated inferiorly to the endoscope. A wide anterior sphenoidotomy is preferred to allow sufficient workspace to target the tumor while working around the internal carotid arteries. The sphenoid septae can be utilized as anatomical landmarks for tumor margins when related to imaging studies. The proximal vomer is a reliable anatomical reference for the midline. The sphenoidotomy should be widened until the tuberculum sellae, lateral opticocarotid recesses, clivus, and planum sphenoidale are identified.

Sellar Phase

The appearance of the sellar floor can vary considerably in the setting of recurrent disease. Depending on the thickness of the sellar floor, a Smith-Ferris rongeur or a microdrill with diamond burr may be needed to penetrate the bone and expose the sellar dura. Bone thickness can be associated with the tumor type, as patients with acromegaly have thicker bone due to hypertrophy [20]. Of note, a suboptimal opening at the sphenoid keel or sella can contribute to subtotal exposure and removal of an otherwise accessible tumor, and is often identified during repeat transsphenoidal operations [23]. Therefore, a wide sphenoid opening and sellar floor exposure, ranging from one cavernous sinus to the other and from the sellar floor to the tuberculum sella is crucial for optimal resection. The most reliable intraoperative midline markers are the vomer, superior sphenoid rostrum, and bilateral parasellar and clival carotid protuberances [24]. One should not rely on the sphenoid septae as a landmark for midline trajectory as large septations often arise posteriorly over the carotid arteries. CT imaging can provide a roadmap for this part of the procedure. The filum of the sella dura, identified as a strand-like dural extension or small vascular dural structure with low-pressure venous bleeding, can also be identified as a midline structure in approximately 50% of the patients [25].

After the dura is completely exposed, micro-Doppler ultrasonography can be used with neuronavigation as well as correlation with preoperative imaging studies to maximize safety and assess the position of the carotid arteries, so as to avoid injury during the durotomy incision. A dural window is created by making a cruciate or X-shaped incision with a retractable blade, and is then carefully widened using a nerve hook or microscissors. If the identification of a cleavage plane is difficult, a micro-Doppler probe can be used to insonate major intradural vessels to define a safe route for dural opening [1]. A subdural plane should be established over the tumor or pituitary gland, although adhesions may be encountered in the case of repeat transsphenoidal surgery. Care must be taken not to enter the dural leaflets, which can result in brisk bleeding from entering the cavernous or intercavernous sinuses.

Tumor Removal

Tumor removal proceeds in a similar fashion, regardless of whether a microscope or endoscope is used. However, the endoscope offers the advantage to directly visualize tumor removal from the cavernous sinus walls and suprasellar space. For a typical macroadenoma, our practice is to follow the capsule by loosening the tissue with a ring curette, starting with the inferior aspect of the tumor then working toward the lateral components, while staying medial to the cavernous sinus. Saving the superior part of the tumor for the end of the dissection helps to prevent the diaphragm sellae and arachnoid from prematurely descending into the sella and becoming an obstacle during dissection by entrapping the residual tumor. Additionally, intraoperative CSF leaks are more common along the arachnoid folds located in the anterior superior portion [19]. A concerted effort should be made to preserve the normal pituitary tissue, which relies on closely inspecting preoperative postcontrast coronal MRI to identify the location of the normal gland, when possible. In large, invasive,

and recurrent adenomas, the normal pituitary gland may be impossible to identify on preoperative imaging, but intraoperatively may be distinguished from the tumor by its yellow appearance and its firmer, stringy consistency.

Tumor debulking techniques may vary based on the consistency of the tumor. Suction and ring curettes can be used on a majority of pituitary tumors, and a minority of firm and fibrous adenomas may require the use of ultrasonic or side-cutting aspirators. Gentle counteraction can be achieved with suction in the left hand while dissecting or debulking with the right hand. Any maneuver more forceful than gentle curetting should be avoided as this may cause trauma to adherent fragments, especially in fibrous tumors. One should exercise great caution when following the tumor into the cavernous sinus or portions that involve the diaphragma. Decompression of the tumor from the intrasellar portion frequently facilitates prolapse of the suprasellar tumor component. With patience, the natural pulsations of the operative field may help the tumor to descend further. Descent of the suprasellar portion of the tumor can also be achieved with a Valsalva maneuver or jugular vein compression. If significant suprasellar extension still remains, some have advocated the insertion of air or lactated Ringer's solution (15–20 ml) into a subarachnoid lumbar catheter to facilitate the tumor's descent, although we rarely find this technique necessary [26, 27]. If possible, facilitating the descent and resection of residual suprasellar tumor should be performed before the onset of an intraoperative cerebrospinal fluid (CSF) leak, and cottonoids can be used to gently prop up and protect any visible arachnoid when resecting the tumor superiorly.

In Cushing's patients, hypertrophy of the circular sinus [28] can result in increased bleeding. Following tumor resection, the operative gutters should be checked for residual tumor [29]. Angled endoscopes (30 or 45°) can also be used to examine the parasellar regions for tumor residual or for CSF leaks.

Microadenomas, and particularly ACTH microadenomas, may not be directly visualized on MRI or found intraoperatively, and therefore require a wider exposure of the entire sella and systematic search through normal gland. The goal is to find a plane for en bloc resection of the tumor, preferably by identifying and working around a pseudocapsule, without compromising the residual portion of the pituitary gland. The pituitary gland should be mobilized with subdural dissection and release of the lateral wings. A transverse incision is then made into the pituitary gland, and lateral pressure can be applied to help deliver the microadenoma into the operative field. Once its location is determined, the cavity, pseudocapsule, and extracapsular region can be removed with a small ring curette and cup forceps.

Image Guidance

Intraoperative image guidance can be an important adjunct during surgery, especially for repeat operations where the normal anatomical landmarks may be disrupted. The use of intraoperative MRI (iMRI) has been shown to improve gross-total resection (GTR) rates. Berkman et al. retrospectively analyzed the use of iMRI on repeat TSS for 109 patients with NFPA with a mean follow-up of 2.2 ± 2.1 years [30]. The authors found that additional resection was possible in 67–69% of the patients, resulting in a GTR rate of 49% for invasive tumors and 75% for

noninvasive tumors. Other studies have reported higher GTR rates (88%) when including both first-time and repeat operations in their analysis [31, 32]. While operative time has been prolonged by an average of 20–30 min for the utilization of the iMRI, an increase in complication rates has not been reported.

Other adjunctive imaging modalities have also helped play a role in transsphenoidal resections. The utilization of indocyanine green fluorescence has been shown to help distinguish pituitary tumors from normal tissue, thereby potentially facilitating a more complete resection while minimizing the risk of injury to the surrounding structures [33]. Intraoperative scanning of the pituitary gland with high-frequency ultrasound probes has also been shown to help localize microadenomas not apparent on MRI [34].

Reconstruction and Closure

After removing the tumor and achieving hemostasis, the sella is evaluated for reconstruction and closure. If a CSF leak has not occurred, packing the sellar cavity with Gelfoam is usually sufficient. In the presence of a CSF leak, which is more likely in recurrent disease, some form of graft may be necessary. A graded approach to repairing CSF leaks in TSS can be employed to minimize the incidence of postoperative CSF leaks in most patients (Table 22.5) [35]. At our institution, we use rescue flaps and a similar graded repair methodology while reserving the use of pedicled nasoseptal flaps for high-flow CSF leaks (communicating with the ventricles or cisternal spaces), and in the 2% of patients that develop postoperative CSF rhinorrhea [36, 37]. The use of an absorbable rigid plate to buttress the sellar floor during reconstruction is typically avoided, due to the risk of delayed erosion of the carotid artery and development of a carotid pseudoaneurysm [38].

The aim of the repair is to ensure a watertight closure and prevent prolapse of the chiasm into the sellar cavity. This needs to be accomplished without overpacking the sellar space, which may compress the optic chiasm. A combination of fat, dura, fascia lata, and/or a vascularized nasoseptal mucosal flap can be utilized for the closure. Fat can be harvested from the right lower quadrant or subumbilical region of the abdomen for graft use, or from the lateral thigh if fascia lata is to be harvested.

Table 22.5 Graded approach to CSF leak repair

Grade	CSF leak description	Reconstructive approach
Grade 0	No leak observed	Collagen sponge
Grade 1	Small leak without obvious diaphragmatic defect	Two-layered collagen sponge repair, cyanoacrylate glue with fascia-lata graft
Grade 2	Moderate leak	Intrasellar and sphenoid sinus fat grafts with collagen sponge overlay, cyanoacrylate glue and fascia-lata graft
Grade 3	Large diaphragmatic/dural defect, resulting in high-flow CSF leaks (communicating with the ventricles or cisternal spaces)	Intrasellar and sphenoid sinus fat grafts with collagen sponge overlay, cyanoacrylate glue, pedicled nasoseptal flaps and CSF diversion

Modified from Esposito et al. [35]

The pedicled, nasal-septal flap is commonly harvested in collaboration with an otolaryngologist when a high-grade CSF leak is anticipated [37]. In repeat TSS, the elevation of a nasoseptal mucosal flap may be challenging due to prior resection of the nasal septum, nasal-septal perforations, nasal-septal deviations, and scar tissue. A variety of techniques can then be used to reconstruct the sellar floor, of which we prefer a two-layer, fascial apposition method [39]. For the purposes of large, recurrent macroadenomas with high-grade CSF leaks, this is performed by packing the sella turcica with fat, developing a two-layer (inlay and overlay) fascial apposition dural repair, then using a pedicled nasoseptal flap. Although the evidence for using a lumbar drain to decrease postoperative CSF leaks is unclear [40], we routinely use lumbar drains in repeat operations where high-grade CSF leaks are encountered.

Careful attention is then paid to the anatomical and physiological restoration of the nasal portion. Hemostasis is achieved, and the nasopharynx is suctioned out. The middle turbinates are then medialized into their normal anatomical position. Although not utilized in a majority of direct approaches, bilateral endonasal packing can also be used (especially in extended approaches) and further secured with a gauze moustache dressing as needed.

Postoperative Care

Postoperative follow-up should include serial visual assessment and monitoring of endocrine functions and metabolic status (Table 22.4). Immediate visual assessment of the patient during postoperative recovery is critical to rule out overpacking of the sella. Cautious postoperative monitoring of fluid and electrolyte balance is mandatory, as the diagnosis of diabetes insipidus and the need for vasopressin are common developments. An elevated serum sodium level or urine output may indicate diabetes insipidus, which is temporary in most cases. Delayed onset of the syndrome of inappropriate antidiuretic hormone secretion can also occur postoperatively. Obtaining a serum sodium value in 1 week after surgery is helpful in preventing potential complications [41]. Routine postoperative MRI is typically not recommended for standard pituitary adenomas until three months following the operation.

Patients should be monitored for signs of new cortisol deficiency by drawing morning cortisol levels. Morning cortisol levels less than 8 μg/dL are considered low, and patients with these levels should be considered for steroid replacement therapy, depending on the presence of clinical symptoms. Prophylactic antibiotics are administered to patients with nasal packing and to prevent postoperative sinusitis. When appropriate, a provocative tilt test on postoperative exams should be performed before patient discharge to assess the integrity of the CSF leak repair. Most patients are discharged by the second or third postoperative day, and follow-up clinic appointments are scheduled in 1 week with follow-up tests on sodium levels on postoperative day 7. Patients should also follow-up with an ophthalmologist for a formal visual field testing, especially in the presence of preoperative visual deficits. For optimal perioperative and postoperative care, surveillance by an experienced multidisciplinary team is essential.

Complications

As with all surgical procedures, avoidance of potential complications is as important as the treatment of disease. Primary TSS can be performed with mortality and morbidity rates of 0–0.9% and 2.2% respectively [10, 42]. Deaths associated with TSS have mainly been due to postoperative management of hyponatremia, pulmonary embolism, or pneumonia [42]. On the other hand, repeat TSS has been associated with higher complication rates and less favorable outcomes than initial surgeries, with an operative mortality of 1.2–2.5% and complication rates of 22–29% [43, 44]. Mortality due to repeat TSS is mainly associated with CSF fistulas resulting in meningitis, intracranial hemorrhage, or hypothalamic damage. More recently, studies have reported 0% mortality and an incidence of 1.7–23.4% of complications with repeat endoscopic TSS (Table 22.6) [1, 14].

The surgical landscape may be altered when employing a transsphenoidal approach for repeat surgery. These changes can be due to a previously compromised diaphragma, scarring, and adhesions between the tumor, optic structures, hypothalamus, and vascular structures, which increases the risks for injury to surrounding structures [15]. For patients who initially had a TSS, the postoperative adhesions and risk for injury may be lower. Prior treatment with radiotherapy and pharmacologic therapy can induce fibrotic changes that can make repeat resection more difficult. Ultimately, complications must be minimized with gentle surgical dissection, taking great care in avoiding traction on the tumor capsule and adherent structures.

Pituitary dysfunction In most cases, the normal pituitary gland can be identified intraoperatively and pituitary function can be preserved. New postoperative endocrine deficits are more common in repeat surgeries. Permanent diabetes insipidus has been reported in 1.4–7.3% of the patients [14, 43].

Cerebrospinal fluid rhinorrhea Postoperative CSF rhinorrhea is a commonly encountered complication of TSS and can occur in 1.7–9% of the patients following surgery [1, 14, 43]. This can result from penetration of the arachnoid membrane or disruption of the sellar diaphragma during the surgical procedure. In most cases this can be avoided with gentle microsurgical technique; however, it may also be unavoidable due to its disruption by the tumor. Packing the sella as described earlier may help repair the leak intraoperatively and prevent the development of postoperative CSF rhinorrhea. Failure in the repair of CSF rhinorrhea with a lumbar drain may necessitate another surgery for repacking of the sella. Early recognition and treatment of CSF rhinorrhea are important because of the higher risk of meningitis.

Hypothalamus Hypothalamic injury can be caused by direct surgical trauma or postoperative ischemia. This can result in death, coma, diabetes insipidus, memory loss, morbid obesity, uncontrollable hunger or thirst, and disruption of temperature regulation. Traction of the pituitary stalk should be avoided to decrease the risk of this complication.

Table 22.6 Reported incidence of complications in TSS for secondary sellar lesions

Patient Cohort	Zada and Weiss[x] (n = 140) Varied approaches (n, %)	Ed laws [45] (n = 150) Varied approaches (n, %)	Ed laws [12] (n = 81) Endoscopic TSS (n, %)	Cavallo [45] (n = 59) Endoscopic TSS (n, %)
Complication				
Death	2, 1.4	4, 2.7	0, 0	0, 0
Stroke	2, 1.4	2, 1.3	1, 1.2	–
Meningitis	6, 4.3	2, 1.3	–	1, 1.7
CSF leak	8, 5.7	9, 9.0	4, 4.9	
Hyponatremia	6, 4.3	–	–	–
DI—transient	8, 5.7	–	–	–
DI—permanent	2, 1.4	11, 7.3	5, 6.2	–
Visual loss	1, 0.7	4, 2.7	–	–
Bacteremia/Sepsis	2, 1.4	–	–	–
Pneumonia	3, 2.1	–	–	–
DVT/PE	2, 1.4	–	–	–
Cranial nerve palsy	0, 0.0	1, 0.7	2, 2.4	–
Hematoma	1, 0.7	2, 1.3	1, 1.2	1, 1.7
Carotid artery injury	3, 2.1	–	,–,–	–
Hydrocephalus	1, 0.7	–	–	–
Hypopituitarism (new)	–, –	13, 8.7	–	–
Epistaxis	1, 0.7	–	2, 2.0	–
Sinusitis	3, 2.1	–	5.1	–
Abdominal hematoma or infection	2, 1.4	–		–
Septal perforation (new)	–	2, 1.3		–
Other	11, 7.9	–	–	–
				–
Total complications	44, 31.4	50, 31.6	19, 23.4	2, 3.4

The data on patients and percentages were extracted, from Zada and Weiss series of 140 patients undergoing transsphenoidal surgery for secondary pituitary adenomas (unpublished); from Laws et al. [43] and from Laws [14]

Visual disturbances The visual pathway can be damaged by direct surgical trauma, hemorrhage or ischemia of the optic nerve, or chiasm. Visual deficits are more likely to occur after repeat surgery due to the presence of adhesions to the chiasm, thereby predisposing to traction injuries. Visual loss has been observed in 0.7–2.7% of cases [43]. Overpacking of the sella can cause compression of the chiasm resulting in immediate postoperative visual deficits. Postoperative visual loss can also signal the formation of a hematoma in the tumor bed and should be evaluated with emergent neuroimaging. These hematomas can be prevented by meticulous hemostasis during the surgical operation.

Vascular injuries Delayed postoperative bleeding from the mucosal branch of the sphenopalatine artery can occur. If postoperative epistaxis continues to persist, embolization of the internal maxillary artery may be required in rare cases. Cavernous sinus injury can also occur, especially when the tumor is either adherent to the sinus or has invaded the sinus. The intracavernous portions of the carotid arteries are the most sensitive to injury. Resecting tumor that is adherent to the intracavernous carotid artery can result in perforation, avulsion, or subsequent thrombosis of the artery. This can further result in an intracranial stroke, development of pseudoaneurysms, or late-onset carotid cavernous fistulas. These can be avoided by noting the position of the carotid arteries in relation to the sphenoid sinus and tumor on preoperative imaging and routinely frameless neuronavigation and intraoperative Doppler ultrasonography on redo operations. The distance from one carotid artery to another can be quite variable [20], and its evaluation can help determine the operative working distance.

If a carotid injury occurs during the operation, it is important to tamponade the bleeding site with a cottonoid while isolating the specific location of arterial injury using a large-bore suction. Communication with anesthesia is paramount in order to maintain a stable blood pressure and confirm that blood is available in the operating room. During repeat surgeries, the surgeon may not have the bony confines to help tamponade the injury. The operative site should be sufficiently packed and closed in a timely fashion, and the patient should be immediately taken to the angiography suite. A potential pitfall is to assume that the bleeding stopped intraoperatively, as additional decompression may allow the bleeding to restart. Patients with intraoperative carotid injuries should be followed closely for the development of carotid pseudoaneurysms, as they are extremely labile and can cause fatal epistaxis or strokes.

Sinonasal complications The incidence of postoperative sinusitis can be reduced by giving prophylactic antibiotics. Mucoceles can develop due to the inadequate removal of mucosa from the sphenoid sinus. If using a speculum, care should be taken to open it carefully as aggressive opening can result in diastasis of the maxilla or fracture of the medial orbital wall. Nasal septum perforations are more common in reoperations. Technical errors in handling the nasal mucosa, nasal septum, and nasal spine may result in cosmetic and functional deficits that can be significantly distressing for the patient. The surgeon can minimize nasal and sinus complications by using a direct endonasal route while minimizing mucosal dissections [10].

Outcomes

Incomplete tumor removal commonly results in regrowth of the tumor. Recent case series have demonstrated a gross total removal (GTR) of recurrent pituitary adenomas using endoscopic TSS in 60.5–62.7% of cases [1, 14]. Cavallo et al. retrospectively analyzed 59 patients with a recurrent pituitary adenoma who underwent surgery using an endoscopic endonasal transsphenoidal approach. The authors achieved GTR in 37 cases (62.7%). Of the secreting adenomas, the overall

remission rate of endocrinological disease was 33.3% (6 of 18 patients). In a subgroup analysis, Cavallo et al. found that GTR was highest in patients who previously underwent a microsurgical transsphenoidal approach (74.2%; 23 of 31), whereas patients who previously underwent an endoscopic endonasal approach (59.1%; 13 of 22) or transcranial approach (16.7%; 1 of 6) had lower rates of GTR. This may be attributed to the improved visualization and exposure provided by the endoscope, in which the residual tumor left in place following an endoscopic TSS may be equally unresectable during a second TSS, as compared to patients who have undergone prior microscopic TSS.

Nonfunctioning Pituitary Adenomas Given that these tumors are not hormonally active, primary outcomes of interest include postoperative pituitary function, visual function, extent of resection, and recurrence rates following repeat surgery. Chang et al. retrospectively analyzed 81 patients who underwent a second microsurgical transsphenoidal resection of an inactive pituitary adenoma at one institution during 1970–2001 [44]. Of the 49 patients with preoperative visual deficits, 39% experienced improved vision. Of the 29 patients with preoperative anterior pituitary dysfunction, 35% recovered function with a second surgery. Of the patients with greater than two-year follow-up, 8% demonstrated a clinically significant recurrence that required additional treatment. Cavallo et al. retrospectively analyzed 41 patients with a recurrent nonfunctional pituitary adenoma who underwent surgery using an endoscopic endonasal transsphenoidal approach [1]. Of the 29 patients with preoperative visual deficits, 72.4% of patients demonstrated improvement while there were no changes in the other 27.6%. Of the 12 patients with preoperative pituitary dysfunction, 33% improved, and there were no changes in 66% of the patients. However, 3/41 patients developed new postoperative endocrine symptoms. In both microsurgical and endoscopic approaches, a decline in preoperative visual function was not observed [1, 44]. Overall rates of visual improvement and hormonal axis recovery are lower following repeat TSS than primary TSS.

Cushing's Disease In hyperfunctioning corticotroph adenomas, remission is defined as a normal postoperative 24-h urine free cortisol or continued need for glucocorticoid replacement after surgery. Overall, remission after repeat transsphenoidal surgery with or without adjuvant therapy for ACTH adenomas has been reported in 50–88% of the patients, with long-term control rates of 51.3% and 66% in macroadenomas and microadenomas respectively [2, 14, 45]. Patil et al. retrospectively analyzed 36 patients with recurrent Cushing's disease who underwent repeat TSS for resection of a pituitary corticotroph adenoma at one medical center from 1992–2006 [2]. Patil et al. found that patients with repeat TSS for recurrent Cushing's disease were 3.7 times more likely to fail achieving remission when compared to patients undergoing first-time TSS (odds ratio, 3.7; 95% confidence interval, 1.8–7.8). Remission occurred in 22 (61%) of the 36 patients. During the same time period, remission was achieved in 289 (85.5%) of the 338 patients who underwent first-time TSS for Cushing's disease. The authors also found that adjuvant therapy with stereotactic radiosurgery, adrenalectomy, and ketoconazole therapy increased remission to 30 (83.3%) of the 36 patients.

Acromegaly Numerous studies reporting outcomes following repeat surgery for recurrent or persistent acromegaly demonstrated variable success rates, ranging from 19 to 60% [4, 11, 14, 46, 47]. Nomikos et al. retrospectively analyzed 140 patients undergoing repeat TSS and found a remission rate of 27.1% [4]. In the subgroup analysis of noninvasive tumors with a GH level below 40 mg/l prior to the first surgery, the remission rate was found to be higher (38.7%). Yamada et al. retrospectively analyzed 53 patients who underwent repeat TSS for recurrent or persistent GH adenomas and demonstrated a long-term cure rate of 49.1% of the patients at 2–3 weeks postoperatively and in 58.5% of the patients at 1 year [46]. The authors selected patients that either failed or were intolerant to adjuvant therapy, and if their tumor was identified on MRI and was accessible by TSS. Yamada et al. found that age >40 years and tumors without cavernous sinus invasion or without tumor segmentation were independent factors for better surgical outcomes. Wilson et al. retrospectively analyzed 14 patients who underwent repeat endoscopic TSS for acromegaly [47]. Of the 14 patients, 8 (57 %) achieved remission following repeat surgical intervention. The authors found that lower preoperative GH levels were associated with a higher chance of remission.

Summary

Transsphenoidal surgery (TSS) remains the preferred approach for the surgical treatment of most recurrent pituitary adenomas. Primary indications for repeat surgery include visual loss, endocrine abnormalities, or imaging evidence of disease recurrence or progression. There are multiple variations in employing the transsphenoidal approach and each has its selective advantages and disadvantages. The surgeon must be prepared for potential obstacles with visualization or abnormal anatomical relationships that may be encountered during repeat surgeries. A multidisciplinary team consisting of a skull-base neurosurgeon, otolaryngologist, endocrinologist, and ophthalmologist should be formed for optimal outcomes. Complications can include CSF leak, vision loss, hemorrhage, epistaxis, postoperative infection, and, rarely, neurological injury, or death. With proper technique and great caution, the endoscopic endonasal approach is a safe method for resection of recurrent pituitary tumors and is associated with a small incidence of complications.

Acknowledgments We would like to thank Rodrick A. Faccio for editorial assistance.

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Transsphenoidal Surgery for Craniopharyngiomas

23

Kenneth Foxx, Stephen Sandwell, Howard Silberstein, G. Edward Vates, Matthew Miller, Ismat Shafiq, Ekaterina Manuylova, and Laura Calvi

Introduction

Craniopharyngiomas are rare epithelial tumors that arise along the path of the craniopharyngeal duct. They have an incidence of 1.3 per million person years with no sex predilection, and account for 2–5% of all primary intracranial neoplasms. Although commonly thought of as a "pediatric" disease (they account for 5.6–15% of all childhood primary intracranial neoplasms), nearly half of the cases are diagnosed in adults, resulting in a bimodal distribution (peak incidence rates: 5–14 years and 50–74 years of age) [1, 2].

The craniopharyngeal duct is formed by the fusion of an evagination of the neural tube and a matching ectodermal outgrowth from the stomadeum (Rathke's pouch) during weeks 8–9 of gestation. The neural tube process becomes the

K. Foxx, MD
Neurosurgery Resident PGY-5, University of Rochester Medical Center, Rochester, NY, USA

S. Sandwell, MD
Neurosurgery Resident PGY-6, University of Rochester Medical Center, Rochester, NY, USA

H. Silberstein, MD, FACS • L. Calvi, MD
Department of Neurosurgery, University of Rochester Medical Center, Rochester, NY, USA

G.E. Vates, MD, PhD, FACS (✉)
Center for Translational Neuromedicine, University of Rochester Medical Center, Rochester, NY, USA
e-mail: edward_vates@urmc.rochester.edu

M. Miller, MD, FACS
Department of Otolaryngology, University of Rochester Medical Center, Rochester, NY, USA

Department of Neurosurgery, University of Rochester Medical Center, Rochester, NY, USA

I. Shafiq, MBBS
Department of Medicine, University of Rochester Medical Center, Rochester, NY, USA

Department of Neurosurgery, University of Rochester Medical Center, Rochester, NY, USA

E. Manuylova, MD
Department of Medicine, University of Rochester Medical Center, Rochester, NY, USA

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_23

infundibulum and neurohypophysis, while components of Rathke's pouch become the adenohypophysis. The formation of the craniopharyngeal duct connects primitive structures that give rise to the hypothalamus, floor of the third ventricle, infundibulum, neurohypophysis, and adenohypophysis [3]. Craniopharyngiomas are found in the sella, suprasellar space, third ventricle, or span these regions, along the path of the craniopharyngeal duct [2–5].

Craniopharyngiomas most often extend from a suprasellar location in association with the infundibulum [4], and 94% have a suprasellar component [5]. Only a small minority of these tumors will be purely intrasellar (4–5%), and most have both suprasellar and intrasellar components (53–75%). Craniopharyngiomas tend to have irregular borders, and are predominantly cystic in 46–64% of patients, predominantly solid in 18–39%, and mixed in 8–36% [2]. They often abut or adhere to important neurovascular structures located in and surrounding the suprasellar space including the optic apparatus, infundibulum, pituitary gland, floor of the third ventricle, hypothalamus, vessels of the circle of Willis, and perforating vessels that supply these and other structures [4].

Craniopharyngiomas are histologically benign World Health Organization (WHO) grade I tumors, with adamantinomatous and papillary subtypes [6]. The adamantinomatous type accounts for the vast majority of pediatric cases, but may occur at any age, and is thought to arise from epithelial remnants of the craniopharyngeal duct derived from stomadeum destined to form tooth primordia [2, 3]. There are cystic and solid components. The cysts (Fig. 23.1a) contain a yellow-brown, cholesterol-rich fluid, and the solid areas (Fig. 23.1b) consist of palisading columnar cells that form whorls, sheets, and irregular shapes around loosely arranged stellate epithelial cells. Characteristic nodules of "wet keratin" are seen, which are desquamated cells that form large, pale, eosinophilic masses that sometimes contain flecks of calcium. Invasion of surrounding brain tissue can cause piloid gliosis with abundant Rosenthal fibers [2, 3, 6].

Papillary craniopharyngiomas occur almost exclusively in adults, with rare reports of pediatric cases [2]. These are more indolent tumors that are thought to arise from metaplasia of squamous epithelial cell rests that are stomadeum remnants intended to contribute to the buccal mucosa [3]. They are characterized by monomorphous, well-differentiated squamous epithelium growing around a fibrovascular core (Fig. 23.1c, d). Ciliated epithelium and goblet cells may rarely be seen [2, 3, 6]. The papillary type of tumors tend to be more well circumscribed than the adamantinomatous type, and the invasion of surrounding brain tissue by neoplastic epithelium is much less common [2, 7].

Patients present when the tumor reaches a sufficient size to cause dysfunction of surrounding structures or symptoms related to elevated intracranial pressure. One of most common presenting symptoms is visual disturbance, and varies from 55–75% across large series [5, 8–10]. Bitemporal hemianopsia is the most common type of visual field deficit owing to the suprasellar involvement of most craniopharyngiomas, and was present in almost a third of patients in one series [5]. Approximately one- to two thirds of patients will have a history of headaches at presentation [5, 8, 10]. Multiple hypothalamic-pituitary axis deficiency and diabetes insipidus (DI) are common presentation in both children and adults [5, 8–10]. Hydrocephalus is present in some cases and is more common in children than in adults [5, 8]. A variety of other symptoms may be noted including cognitive dysfunction, obesity, lethargy, gait disturbance, and focal neurologic deficits [5, 9, 10].

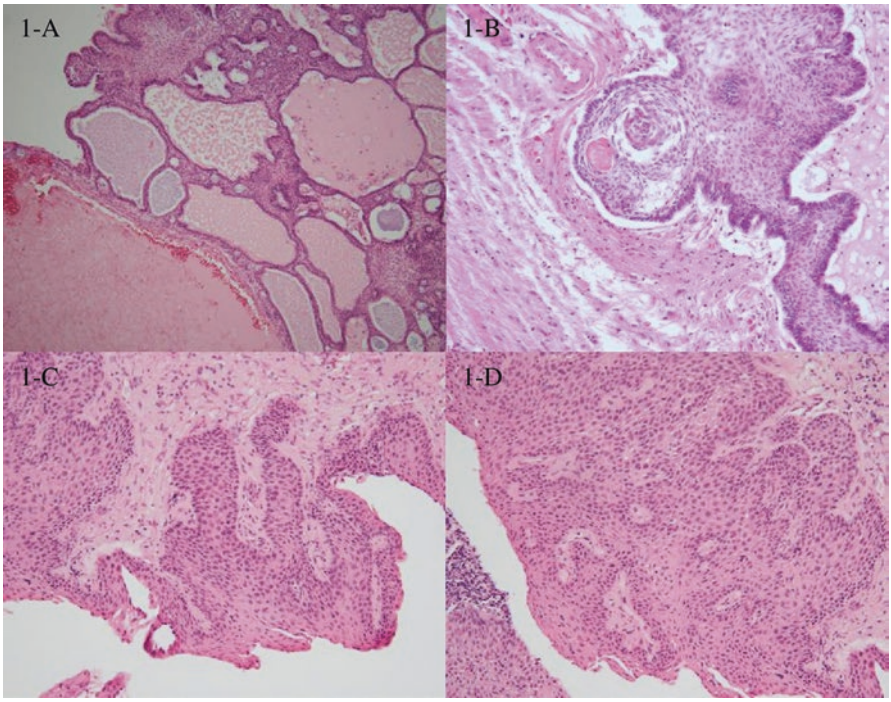

Fig. 23.1 Classic histological appearance of adamantinomatous (**a**, **b**) and papillary (**c**, **d**) craniopharyngioma subtypes

Treatment Strategy and the Endoscopic Endonasal Transsphenoidal Approach

Although benign, craniopharyngiomas are challenging because of their location, local invasiveness, and relationship to adjacent critical neurovascular structures. Surgical intervention is indicated to confirm diagnosis, and for tumors causing neurologic deficits, pituitary dysfunction, obstructive hydrocephalus, or those with growth on serial imaging [11, 12]. Multiple studies have demonstrated a decreased rate of recurrence after gross total resection [5, 7, 9], but this can be accompanied by endocrinologic consequences [14]. In addition, subtotal resection with adjuvant radiation therapy may be just as effective as gross total resection [13, 14]. However, other series have shown no association between treatment strategy and neurologic or endocrine side effects [5, 7]. In our hands, we pursue maximal safe resection followed by adjuvant radiation therapy in the case of residual tumor. This is a particularly important consideration in children, where hypothalamic or pituitary injury can have especially severe consequences [4, 11, 12]. Other adjuvant therapies such

as fenestration of cystic components or placement of an Ommaya reservoir for repeated aspiration may be considered. Intracystic infusion of agents to promote cell death and/or prevent cell division, such as radioisotopes or bleomycin, has also been reported [2].

The first reported transsphenoidal resection of a craniopharyngioma was by Alan E. Halstead in 1909, and later reported by Harvey Cushing in 1910, but transsphenoidal approach was largely abandoned in the first half of the twentieth century. Jules Hardy's use of intraoperative fluoroscopic image guidance and the operating microscope made surgery technically feasible, and with effective antibiotic therapy to prevent surgical infection and the development of effective hormone replacement, patients could be shepherded through surgery safely and effectively [15]. In series published by Edward Laws in 1980 and later in 1994, the transsphenoidal microsurgical approach was restricted to intrasellar or primarily intrasellar tumors with subdiaphragmatic suprasellar extension and enlargement of the sella. Lesions with significant suprasellar extension were still better approached transcranially [15–17].

Extended transsphenoidal microsurgical approach, first described with the operating microscope [18–20], allowed for resection of purely suprasellar lesions by removing the tuberculum sellae and planum sphenoidale. The transsphenoidal approach was an attractive alternative to traditional craniotomy because of the avoidance of frontal and temporal lobe retraction, Sylvain fissure dissection, and decreased manipulation of the optic apparatus and other neurovascular structures [21]. Retraction related injury from contusion and infarction has been estimated to occur in approximately 10% of transcranial skull base operations [22].

The first report of a purely endoscopic endonasal transsphenoidal (EET) approach to the sella was by Jankowski et al. in 1992 [15, 23]. Improvement of endoscopic technology, instrumentation, anatomical knowledge, and experience led to the development of extended endoscopic endonasal transsphenoidal (EEET) approaches for predominantly suprasellar tumors [4, 11, 15, 24]. The visualization offered by the endoscope is superior to the microscope because the light source and lens are closer to the surgical target, and the field of view is not limited by long, narrow retractors. With angled endoscopes, the surgeon can "view around corners" in a way that is not possible with the operating microscope. The improved visualization afforded by the endoscope allows for higher rates of gross total resection with less risk to surrounding neurovascular structures. EET approaches are also mucosa-sparing, whereas microscope-based extended approaches require sublabial incision and submucosal dissection [21], although the use of a mucosal flap may balance this issue out.

Gross total resection rates with EET approaches are comparable to those achieved with transcranial techniques [8, 10, 21, 25, 26]. One meta-analysis showed a significantly greater rate of gross total resection in patients undergoing EET approaches (56.2%) compared to transcranial routes (48.3%). There was a significantly greater rate of visual improvement in patients that underwent resection with an EET approach (56.2% compared to 33.1%). No postoperative seizures occurred in patients undergoing EET resection, whereas there was an 8.5% rate of postoperative seizures in

the transcranial group. There was a significantly higher incidence of postoperative cerebrospinal fluid (CSF) leak in the EET group (18.4% compared to 2.6%) [27]. The increased risk of postoperative CSF leak is also apparent across series [8, 10, 21, 25, 26], but improved closure techniques and vascularized reconstruction have addressed this lingering concern [8, 11].

Preoperative Evaluation and Imaging Findings

The evaluation of any patient begins with a detailed history and neurologic exam, with careful documentation of any deficits. Any patient with visual complaints, visual deficits identified on exam, or evidence of optic chiasm compression on imaging should undergo a formal neuro-ophthalmologic examination. All patients should undergo a thorough endocrine evaluation, directed by an experienced endocrinologist, to include fasting morning cortisol, adrenocorticotropic hormone, thyroid function testing, follicle-stimulating hormone, luteinizing hormone, growth hormone, insulin-like growth factor-1, free and total testosterone, estradiol, prolactin, serum sodium, and urine specific gravity [4, 11, 12]. Endocrinologic assessment is especially important in pediatric patients, who may also present with signs and symptoms of hypothalamic dysfunction [2]. Glucocorticoids (GC) treatment should be initiated in patients with hypothalamic-pituitary-adrenal (HPA) axis deficiency preoperatively. Thyroid hormone replacement can be considered in selected cases before surgery. In patients with cognitive dysfunction, tumors causing significant mass effect, or with extensive involvement of the hypothalamus, frontal, or temporal lobes, neuropsychological testing may be valuable, but is seldom performed at most centers [11].

Magnetic resonance imaging (MRI) provides the greatest detail about a tumor's location, character, and association with surrounding structures [11]. The imaging hallmarks of craniopharyngioma are calcification, cyst formation, and contrast enhancement of the solid portion of the tumor (Figs. 23.2 and 23.3). A cystic component is identified on imaging in approximately 85% of cases, and calcification, which may be nodular or rim-like, is seen in about 80% of cases. Tumors with higher protein content tend to be more hyperintense on T1 weighted imaging (WI) and those with lower protein content tend to be more hypointense, although some tumors with ultra-high protein content may be hypointense due to increased viscosity. They are generally hyperintense on T2WI [28]. The relation of major vascular structures to the tumor can usually be assessed on T2WI, but further angiographic studies may be obtained if needed. Coronal T2 fluid attenuated inversion recovery (FLAIR) sequences are often helpful for assessing the degree of hypothalamic involvement [11].

Computed tomography (CT) imaging is helpful for assessing characteristics of the tumor as well as for operative planning. CT clearly demonstrates calcifications within the tumor, whereas MRI is relatively insensitive. Cysts can also sometimes be more easily identified on CT compared to MRI, as cystic fluid is usually low

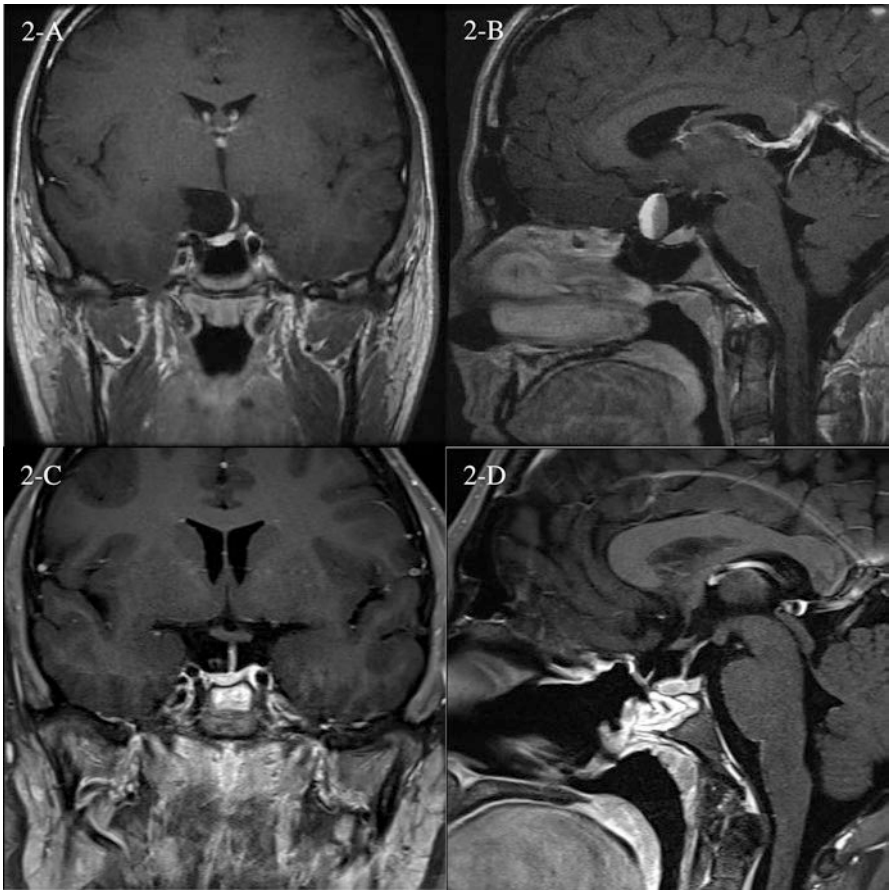

Fig. 23.2 Preoperative coronal (**a**) and sagittal (**b**) T1 weighted images with contrast in a patient with a Kassam type I craniopharyngioma. Postoperative coronal (**c**) and sagittal (**d**) T1 weighted images with contrast in the same patient demonstrating gross total resection

density on CT, but may be of variable intensity on MRI [28]. CT is also useful for assessing the degree of pneumatization, size, and shape of the sphenoid sinus, as well as the location of the septations within the sinus [11].

Craniopharyngioma Classification and Preoperative Planning

Multiple classification systems have been developed based on the location of the craniopharyngioma relative to the optic chiasm [29], diaphragma sellae [30], third ventricle [31], and infundibulum [24], and have important implications for both transcranial and endoscopic surgical planning. The scheme developed by Hoffman

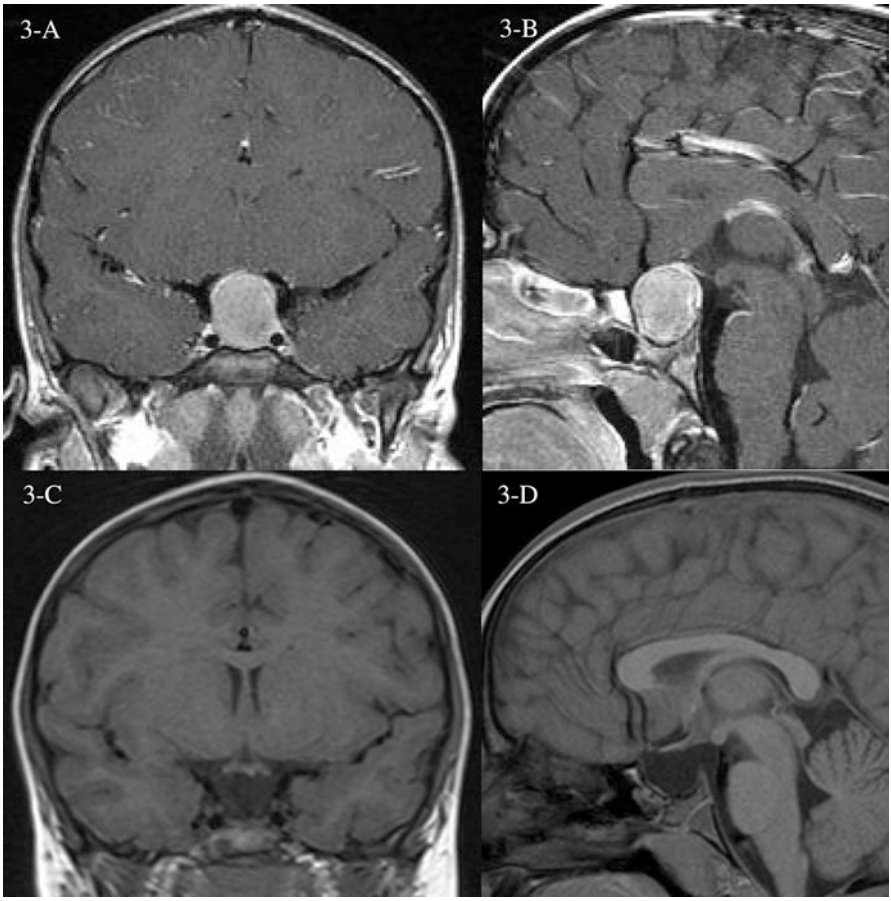

Fig. 23.3 Preoperative coronal (**a**) and sagittal (**b**) T1 weighted images with contrast in a patient with a Kassam type II cranipharyngioma. Postoperative coronal (**c**) and sagittal (**d**) T1 weighted images without contrast in the same patient demonstrating gross total resection

divided tumors into sellar, prechiasmatic, retrochiasmatic, and giant tumors that grew both forward between the optic nerves (ONs) and backward into the posterior fossa. Prechiasmatic tumors can usually be approached with a small right frontal bone flap and subfrontal approach accessing the tumor between the optic nerves. Retrochiasmatic tumors require an extended pterional approach, a pterional flap extended to the medial frontal area, with the tumor approached either through the lamina terminalis, opticocarotid triangle, or both [29]. Wang et al. built upon the Hoffman system by noting that prechiasmatic lesions tended to be subdiaphragmatic, whereas retrochiasmatic lesions tended to supradiaphragmatic. The authors noted that some prechiasmatic tumors could be approached via the transsphenoidal route in the setting of a favorable sella [30].

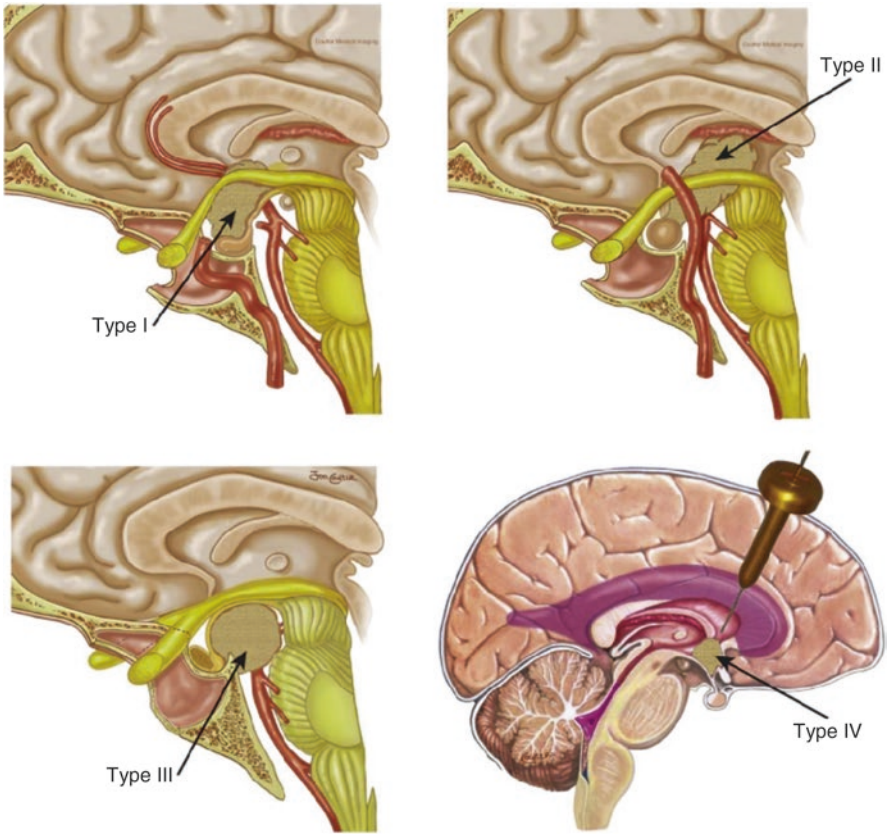

Fig. 23.4 Types of craniopharyngiomas (Reprinted from Schmidek and Sweet *Operative Neurosurgical Techniques*, Vol. 1, sixth edition, Daniel M. Prevedello, Domenico Solari, Ricardo L. Carrau, Paul Gardner, Amin B. Kassam, Endoscopic Endonasal Approach for Craniopharyngiomas, 303–310, 2012, with permission from Elsevier)

For the purposes of endoscopic approaches to craniopharyngiomas, we have found the classification system developed by Kassam et al. to be the most useful [11, 24]. Type I tumors are preinfundibular, type II tumors are transinfundibular, type III tumors are retroinfundibular, and type IV are isolated third ventricular tumors (Fig. 23.4). Craniopharyngiomas demonstrate diverse growth patterns, and are often not restricted to a single compartment. Some large tumors can occupy the entire prepontine cistern, suprasellar cistern, or both. It is useful to identify the predominant location of the solid component of the tumor and use it as the primary target, which determines the specific EEET approach to be used. Kassam et al. recommend using volume-acquisition T1WI contrast-enhanced MRI sequences, such as those used for image guidance, to identify the location of the infundibulum

[24]. Since this classification was developed for suprasellar craniopharyngiomas, primarily sellar subdiaphragmatic lesions are not classified with this scheme.

Type 1 preinfundibular tumors (Figs. 23.2 and 23.4) are bounded posteriorly by the infundibulum, inferiorly by the diaphragma sellae, and laterally by the internal carotid arteries (ICAs). These tumors are usually subchiasmatic and tend to displace the optic chiasm superiorly and posteriorly. The anterior communicating artery (ACoA) complex is usually separated from the tumor by the chiasm, but these tumors can invade the prechiasmatic cistern and adhere to the vessels of the ACoA complex [11, 24].

Type II transinfundibular tumors (Figs. 23.3 and 23.4) infiltrate and grow along the axis of the infundibulum, widening its diameter. These lesions have the same posterior, inferior, and lateral boundaries as type I lesions, but can extend into the third ventricle through the tuber cinereum because of their infiltrative growth along the infundibulum. The rostral boundary of the intraventricular portion of the tumor is the anterior hypothalamus and lamina terminalis. These tumors can also have exophytic extensions into the subchiasmatic space [24].

Type III retroinfundibular tumors (Fig. 23.4) are further subdivided based on the presence of extension superiorly (IIIa) into the third ventricle or posteriorly and inferiorly (IIIb) into the interpeduncular and prepontine cisterns. These tumors are bounded anteriorly by the infundibulum, and usually penetrate the membrane of Liliequist posteriorly to involve the basilar apex, posterior cerebral arteries (PCAs), and perforators of the first segment (P_1) of the bilateral PCAs. The tumor can then extend superiorly into the third ventricle with midbrain involvement, or inferiorly with adherence to the oculomotor nerve, superior cerebellar arteries, or even more caudal structures. The lateral boundary of all type III tumors are the oculomotor nerves and posterior communicating arteries [11, 24].

Types I, II, III, and isolated sellar tumors may be approached by the EET route. Type IV tumors (Fig. 23.4) are isolated to the third ventricle and are not easily accessed with the EET approach [19]. These lesions can be better accessed with traditional craniotomy and transcallosal, transcortical, transventricular, or translamina terminalis approaches [31]. The lateral limit of the EET approach is the ICA bifurcation, and craniotomy is usually more appropriate with tumors that have significant extension beyond this point. Relative contraindications to the EET approach are very large tumors with a significant solid component, multicompartment location, significant vascular encasement, and extensive calcification [11].

Preoperative CT imaging is helpful for assessing the pneumatization of the sphenoid sinus. Sphenoid sinus type is classically divided into conchal, presellar, and sellar based on the degree of pneumatization. The conchal type sinus is very small and separated from the sella by cancellous bone that is approximately 1 cm thick. The presellar type sinus does not penetrate beyond a plane perpendicular to the tuberculum sellae and there is no appreciable sellar bulge within the sinus. The sellar type sinus extends to and beneath the sella with a thin sellar wall [32]. Some authors use the term postsellar sphenoid sinus to refer to highly pneumatized types

that extend posterior to the sella and into the dorsum sellae. In adults, the sellar type is most common and the conchal type is rare. A very highly pneumatized sphenoid sinus can distort anatomical landmarks and place the ICA and ON at risk. A poorly pneumatized sphenoid sinus can make the EET approach more difficult, but modern instrumentation and neuronavigation make traversing even conchal type sinuses possible [33].

This is particularly important in the pediatric population, as pneumatization of the sphenoid sinus is a progressive process beginning at 2 years of age and reaching maturation around 14 years of age [33]. Developmental pneumatization of the sphenoid sinus follows an inferior-to-superior and medial-to-lateral pattern at a relatively slow pace. Pneumatization patterns correlate with age, such that conchal type is most common and sellar type the least common in 2–4 year olds, with the exact opposite being true at maturation. A conchal type sinus is correlated with a narrow intercarotid distance and a tight working angle regardless of the patient's age. The size of the nasal aperture increases slowly with age, potentially restricting endoscopic access in the very young [34]. Conchal type sphenoid sinus, narrow intercarotid distance, and very young age are all relative contraindications to the EET approach [11]. Some centers perform EEET approaches in all age groups with resection of the middle turbinate to increase access on a case-by-case basis [34], but in our hands we would approach these lesions transcranially.

Careful attention to the position of septae within the sphenoid sinus and their relation to the ICAs is important [11, 35]. Most sphenoid sinuses have one major septum, located off midline, but there is considerable variability. There may be two major septae, and there are usually many minor septae present [36]. If a septum is located over or lateral to the ICA, this must be noted and care must be taken during intraoperative removal. Excision of septae that insert directly over the ICA is particularly dangerous and can lead to vessel laceration [35].

When a posterior ethmoidectomy is to be performed as part of an EET approach, the ethmoid sinus should also be examined on preoperative CT imaging. The lamina papracea should be evaluated for dehiscence, which predisposes the patient to orbital injury during an endoscopic approach. The degree of pneumatization of the ethmoid sinus should be appreciated. Highly pneumatized posterior ethmoid air cells can extend into the sphenoid sinus and are called Ondi cells. These air cells can contain the ON or ICA, and must be appreciated prior to surgery [35].

Endoscopic Endonasal Transsphenoidal Surgical Technique for Craniopharyngiomas

As mentioned at the beginning, treatment of craniopharyngiomas requires a multidisciplinary team, and in surgery the team consists of an otolaryngologist and a neurosurgeon. The otolaryngologist usually performs the nasal and sinus exposure, and the neurosurgeon performs the intradural portion of the procedure, using two-hand technique, guided by the endoscopist [11, 24]. One-handed technique has been described, and other surgeons may be comfortable with this approach, but in our

hands patients benefit from having the neurosurgeon's undivided attention and both hands focused on tumor resection; the otolaryngologist has greater daily experience navigating the paranasal sinuses with an endoscope, and brings that valuable skill set and assistance to the field.

Preparation and Positioning

Following induction of general anesthesia, a lumbar drain is placed. Small sellar subdiaphragmatic tumors are unlikely to have postoperative CSF leaks or require diversion. However, patients undergoing EET approaches with wide arachnoid cistern opening, possible entry into the third ventricle, or with preoperative hydrocephalus benefit from a lumbar drain [35]. Injection of intrathecal fluorescein may aid in visualizing violation of the arachnoid cisterns and can be helpful during reconstruction [12].

The patient is positioned supine with the head either in rigid pin fixation or on a headrest. Some surgeons prefer to turn the patient's head 5–15° toward the patient's right side where the operative surgeon stands [24, 37], but in our hands with a two surgeon approach it is better to keep the patient's head midline. The head is extended 10–15° to prevent instruments and the endoscope from being restricted by the patient's chest. EET approaches will have a more anterior trajectory through the planum and tuberculum sellae than pure sellar approaches, and may require more extension depending on the patient's habitus [37]. Neuromonitoring may be initiated and continued throughout the procedure if desired [24]. Neuronavigation based on preoperative MRI and CT studies is required for EET approaches. The patient is registered with the neuronavigation system and the screen is positioned such that both surgeons can see both navigation and endoscopic views easily [37].

An arterial line should be placed for close hemodynamic monitoring during the procedure; significant blood loss is unlikely, but if carotid injury is encountered there is little time to gain accurate hemodynamic monitoring and other "excitement" requires the surgical teams' undivided attention. Additionally, most patients will require careful fluid management and frequent laboratory testing that makes an arterial line a wise investment up front. The nasal cavity may be pretreated with cocaine pledgets or Afrin for decongestion [12]. Appropriate perioperative antibiotics and stress dose methylprednisolone are administered. The midface is usually prepared with Betadine [24]. The abdomen and lateral thigh are also prepared if fat and fascia lata graft harvest is anticipated, respectively. Prior to beginning the nasal approach, lidocaine with epinephrine is injected into the nasal rostrum and septum [12].

Nasal and Sinus Exposure

Most authors describe beginning the nasal exposure with a 0°, 18-cm long, 4-mm endoscope (Karl Storz; Tuttlingen, Germany) [11, 12, 24, 37]. A 2.7-mm endoscope may be used in patients with narrow nostrils [38]. In the case of an EEET approach, the

procedure begins with the elevation of a nasoseptal flap based on the nasoseptal artery [38]. When tumors are primarily sellar and infradiaphragmatic, a nasoseptal flap is usually not necessary. The bilateral middle and inferior turbinates are lateralized. The middle turbinate may be removed, usually on the right, depending on tumor location, size, or need for additional room to accommodate instruments or the endoscope [11, 24].

The size of the nasospetal flap is designed for the anticipated defect, but in general "bigger is better." Redundant flap can be trimmed, but no amount of time or tension will make the flap grow if it is inadequate. Two parallel horizontal incisions are made in the nasal septum, one over the maxillary crest and the other a few centimeters below the superior limit of the septum, such that olfactory epithelium is not incised. The superior incision is extended laterally and slightly inferiorly, at the posterior aspect of the septum, such that it crosses the rostrum of the sphenoid sinus and passes through the ostium. At the posterior nasal septum, the inferior incision is extended superiorly along the septum, then laterally to cross the posterior choana below the sphenoid sinus. The anterior aspect of the two horizontal incisions is connected with a vertical incision. Elevation of the flap proceeds anterior to posterior with preservation of the posteriorly located nasoseptal neurovascular bundle. The mucoperiosteum and mucoperichondrium are elevated with the flap to allow coverage of large defects during reconstruction. The flap is tucked into the nasopharynx until the reconstruction portion of the procedure, taking care not to strangulate the vascular supply [38].

The bilateral sphenoid ostia and exposed posterior nasal septum are then identified. Approximately 1–2 cm of the posterior nasal septum attachment to the sphenoid rostrum, comprising the vomer and associated cartilage, is removed. Wide bilateral sphenoidotomies are then made, beginning at the ostia, such that a large single working cavity is created. If an extended approach is being undertaken, bilateral posterior ethmoidectomies are then performed with the anterior extent no further than the location of the posterior ethmoidal artery. This exposes the planum sphenoidale, and is done for all tumors that are not primarily sellar and subdiaphragmatic. Although the tumor may not extend over the planum, the posterior ethmoidectomy and subsequent removal of the planum allows for the anterior trajectory needed to reach the suprasellar region, limits bony impingement on instrumentation, and widens working angles. Care must be taken not to puncture the cribriform plate during this part of the exposure. The opening in the anterior wall of the sphenoid sinus is then enlarged circumferentially and all septae are removed up to their attachments on the anterior and superior walls. When nasoseptal flap closure is anticipated, the sphenoid mucosa must be completely removed to prevent mucocele formation and provide a bony surface for the vascularized flap to adhere to. Removal of the mucosa also exposes important bony landmarks to guide the remainder of the surgery. Once complete, the exposure extends from the ethmoid sinus anteriorly to the clival recess posteriorly, and gives a panoramic view of the planum sphenoidale, tuberculum sellae, and sella [11, 12, 19, 33, 35].

During the later stages of the exposure, it may be necessary to use a longer 30-cm endoscope [12]. Use of a 30°-angled endoscope may also be helpful, so that the tip can be removed from the working area. This also avoids the need to switch between 0° and 30° endoscopes to provide sufficient superior and lateral views [11].

Skull Base Exposure and Tumor Resection

The remainder of the skull base exposure and the tumor resection is performed by the neurosurgeon, standing on the patient's right, using two-handed technique, and guided by the endoscopist. The endoscope is generally placed through the left nostril and held in a superior location, so that a suction tip can be passed below the endoscope to the dependent part of the surgical field [24], but positioning of the endoscope and instruments is a fluid "dance" made easier when the neurosurgeon and otolaryngologist have extensive mutual experience. Careful use of navigation and knowledge of bony landmarks will guide a safe skull base exposure.

Depending on the degree of pneumatization of the sphenoid sinus, important protuberances and depressions are identifiable to varying degrees. In the case of poorly pneumatized sphenoid sinus, the surgeon must rely solely on navigation until reliable landmarks can be identified. In the midline from rostral to caudal, the posterior part of the cribriform plate, the planum sphenoidale, tuberculum sellae, sella, sellar floor, and clival recess are identified (Fig. 23.5a). Lateral to the sella, the parasellar carotid protuberance, overlying the cavernous ICA, and optic canal are seen [11, 24, 37, 39]. The lateral opticocarotid recess (lOCR) is a depression inferior to the optic canal and lateral to the carotid protuberance. The pneumatization of the lOCR often extends into the optic strut and may extend into the anterior clinoid [39]. Although it is not involved in the exposure, the lOCR is useful for identifying the location of the medial opticocarotid recess (mOCR), which represents the ventral aspect of a pneumatized middle clinoid process [11]. The middle

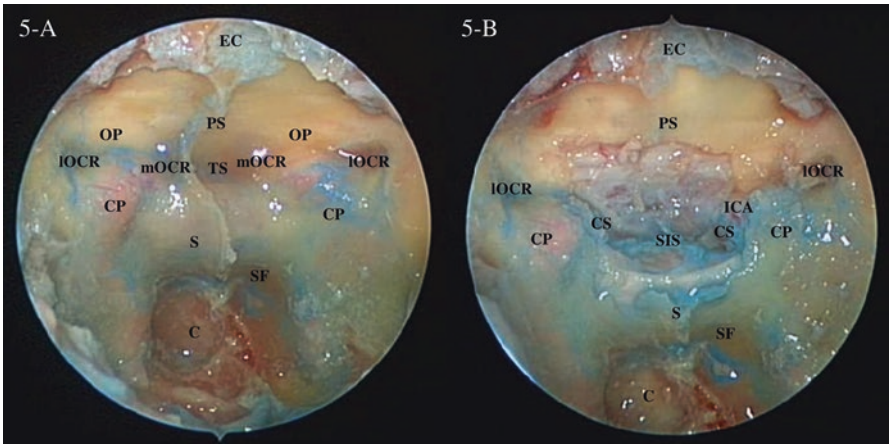

Fig. 23.5 Extended endoscopic endonasal transsphenoidal (EEET) approach in a cadaver prior to (**a**) and subsequent to (**b**) removal of the posterior planum sphenoidale, tuberculum sellae, and superior sellar wall (*EC* ethmoid air cells, *PS* planum sphenoidale, *TS* tuberculum sellae, *S* sella, *SF* sellar floor, *C* clivus, *OP* optic protuberance, *CP* carotid protuberance, *mOCR* medial opticocarotid recess, *lOCR* lateral opticocarotid recess, *CS* cavernous sinus, *SIS* superior intercavernous sinus, *ICA* internal carotid artery)

clinoid process is only present in about 50% of patients and the mOCR is rarely visible as an actual depression, but its location can be identified by surrounding landmarks [39]. It is located at the medial extent of the parasellar carotid protuberance and cavernous sinus, lateral extent of the sella, and inferomedial aspect of the optic canal [11]. Its removal is important for identifying the location of the supraclinoid ICA and ON [39].

The extent of the skull base exposure is determined by the size of the tumor and its location. Primarily sellar infradiaphragmatic tumors can be accessed by a standard endoscopic approach to the sella and removal of the anterior sellar wall, whereas suprasellar lesions require more extensive exposure [11, 24]. It is important to avoid removing too much of the skull base and overexposing the dura, which will lead to brain herniation through the dural incision along the planum sphenoidale, and will complicate the reconstruction. The exposure should be as limited as possible, guided by neuronavigation, while still allowing for successful resection [24].

Regardless of location, the skull base exposure for a suprasellar tumor begins with the removal of the tuberculum and upper half of the sella with exposure of the anterior intercavernous sinus. We thin the tuberculum with an ultrasonic curette and then use a 2-mm Kerrison rongeur to remove the tuberculum extending laterally to the mOCR. We then use a drill or ultrasonic aspirator near the mOCR, where copious irrigation is necessary to prevent injury to the ON. Removal of the middle clinoids widens the exposure to allow early identification of the ON and paraclinoid ICA. This allows the surgeon to work from normal to abnormal structures, and prevents injury to the subchiasmatic perforating vessels and superior hypophyseal arteries. Intercavernous sinus bleeding can be encountered during removal of the upper sella and tuberculum, but this is easily controlled with cottonoids, gel foam, and bone wax [11, 24, 37]. The planum sphenoidale is then thinned if needed, dissected free from the dura and removed with a 2-mm Kerrison rongeur. The falciform ligament is carefully dissected during the exposure to prevent unintentional (and sometimes "hidden") durotomy, and the lateral extent of the exposure is the medial boundaries of the ONs. Removal of the planum may extend anteriorly about 1.5–2 cm if needed, but should not extend past the rostrum of the sphenoid sinus to avoid damaging the cribriform plate, olfactory nerve fibers, and posterior ethmoidal arteries [37].

After the bony removal is complete (Fig. 23.5b), the superior intercavernous sinus should be ligated prior to the dural opening [37]. Prior to sinus isolation or dural opening, we use Doppler ultrasound to localize the bilateral ICAs and avoid injury, particularly in their proximal supraclinoid portion as they course medially [11, 12]. Two small horizontal incisions are made above and below the superior intercavernous sinus in the midline, between the mCORs. Bipolar forceps (specially designed for delivery through the nares) are then used to coagulate the sinus and it is divided with microscissors. The dura is then opened in cruciate fashion extending from the superior intercavernous sinus division point, and the dural leaflets are coagulated for retraction. The diaphragm sella lies behind the superior intercavernous sinus, and may be opened with microscissors to allow access to the sella and inferior retraction of sellar contents (Fig. 23.6a, b) [11].

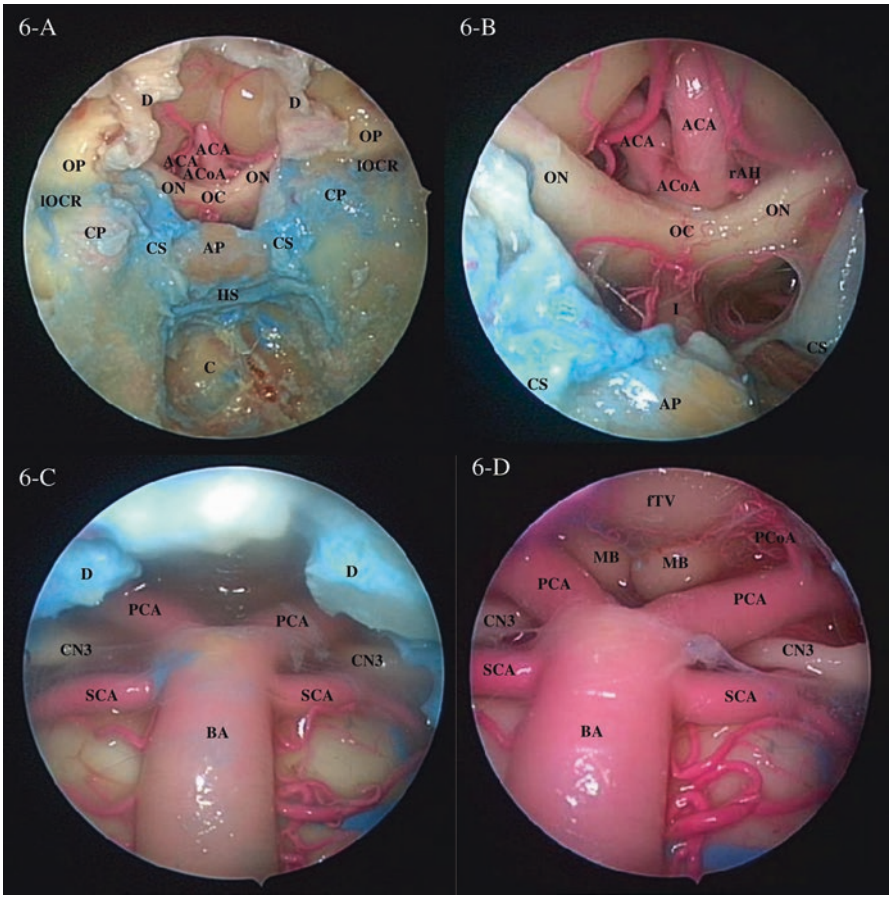

Fig. 23.6 Extended endoscopic endonasal transsphenoidal (EEET) approach in a cadaver with exposure of the suprasellar space (**a**, **b**) and a transclival approach (**c**, **d**) (D coagulated dural edge, *OP* optic protuberance, *CP* carotid protuberance, *lOCR* lateral opticocarotid recess, *ACA* anterior cerebral artery, *ACoA* anterior communicating artery, *rAH* recurrent artery of Heubner, *OC* optic chiasm, *I* infundibulum, *ON* optic nerve, *CS* cavernous sinus, *AP* anterior pituitary gland, *IIS* inferior intercavernous sinus, *C* clivus, *PCA* posterior cerebral artery, *CN3* oculomotor nerve, *SCA* superior cerebellar artery, *BA* basilar artery, *fTV* floor of the third ventricle, *MB* mammillary body, *PCoA* posterior communicating artery)

Type I: Preinfundibular Craniopharyngiomas

Type 1 lesions are usually visible as soon as the dura is opened, and, for the most part, attention is directed to the intracranial space above and in front of the pituitary gland and stalk (making these lesions the most amenable to the transsphenoidal approach because this is a less treacherous space to work). Unless the tumor is sufficiently small, we first incise the capsule and drain any cystic contents before proceeding with debulking and extracapsular dissection. A ringed curette is used to debulk internally, first focusing on the inferior portion of the tumor to eliminate

meningeal feeding vessels early in the dissection and deliver the superior intracapsular contents inferiorly [11, 24]. When the tumor is adequately debulked, the capsule will start to mobilize with gentle microsuction, which allows for traction during extracapsular dissection [24].

Extracapsular dissection should begin at the opticocarotid cistern contralateral to the infundibulum, as this is generally the point of attachment for craniopaharyngiomas. The contralateral opticocarotid cistern is opened and the contralateral ON identified as it enters the optic canal. Dissection along the ON will lead to identification of the contralateral ICA in an inferolateral location. Subchiasmatic perforating vessels will be present along the superior and lateral surfaces of the tumor. Extracapsular dissection then proceeds posteriorly to the optic chiasm [24]. In the case of significant extension into the prechiasmatic space, the tumor is carefully separated from the ACoA complex to avoid injury to perforating vessels or the recurrent artery of Huebner [11]. The tumor is then freed from the inferior surface of the optic chiasm proceeding to the opticocarotid cistern ipsilateral to the infundibulum, with dissection along the ipsilateral ON and subsequent identification of the ipsilateral ICA. The inferior portion of the tumor is now separated from the diaphragma and dura, with careful identification and preservation of the infundibulum posterior to the tumor and the superior hypophyseal arterial supply. The point of tumor attachment to the infundibulum is then sharply divided and the capsule removed [24].

Type II: Transinfundibular Craniopharyngiomas

Unlike type I lesions, which, for the most part, are centered anterior and inferior to the optic apparatus and pituitary stalk, type II lesions are centered right where these sensitive structures exist. Consequently, transsphenoidal approach to these tumors requires a strategy by which these structures can be manipulated safely in order to access tumor around and past them (into the floor of the third ventricle).

In addition to the skull base exposure described for type I lesions, type II lesions require removal of bone over the entire anterior sellar wall with ligation of the superior intercavernous sinus as previously described (Fig. 23.6a, b). This allows for downward retraction of the pituitary gland and the more anterior angle needed to access type II tumors that infiltrate along the infundibulum and extend into the floor of the third ventricle [24].

Type II tumors that transgress the pituitary stalk usually have an exophytic component in the suprasellar cistern, which is encountered first. Once this component is removed (as described for type I lesions), the infundibulum is identified rising through the diaphragma toward the floor of the third ventricle. Type II tumors widen the pituitary stalk as they infiltrate through it. To remove this portion of the tumor and the tumor in the floor of the third ventricle, the stalk can either be transected in a premeditated fashion, or an attempt can be made to preserve stalk function by incising it vertically along the presumed track of the tumor, between blood vessels running in the long axis of the stalk, in order to preserve the hypophyseal portal system and the axons running toward the posterior pituitary. Using a corridor

provided through the stalk by the infiltrating tumor, dissection proceeds by debulking this corridor internally, and then the tumor capsule is sharply separated from the infundibulum starting at the level of the diaphragm and progressing superiorly along the course of the stalk into the floor of the third ventricle, where the tumor often adheres to the anterior hypothalamus in the optic recess [24]. If the tumor extends into the anterior part of the third ventricle, additional bone removal long the planum and opening of the dura provides access to the lamina terminalis. However, pursuit of tumor deep into this part of the third ventricle can lead to hypothalamic injury and is particularly devastating in children [11]. Unless there is a clear and easily exploited plane between the tumor and the wall of the third ventricle, we will not risk hypothalamic injury in pursuit of a gross total resection. Traction on the tumor capsule and bipolar cautery should be avoided [24]; we rely on sharp dissection and address bleeding with hemostatic agents and gentle compression with cottonoids.

Transection of the infundibulum may be required to achieve gross total resection of transinfundibular tumors and is an appropriate anticipated intraoperative "choice" when the patient presents with panhypopituitarism. However, in patients with preserved pituitary function, it may be more reasonable to accept subtotal resection. If transection of the infundibulum is anticipated, it should be discussed with the patient preoperatively and the implications of permanent panhypopituitarism explained [11]. It is important to address with patients (and for pediatric patients, with their parents) the risks to fertility and sexual function in a way that is appropriate and culturally sensitive; this is often best handled by experienced reproductive medicine colleagues, but these referrals must be made before surgery.

Type III: Retroinfundibular Craniopharyngiomas

1. Type I lesions require operating in front of the pituitary stalk and under the ACoA/optic chiasm. Type II lesions require operating around/through the pituitary stalk and around/above/behind the ACoA/optic chiasm to access the third ventricle. Type III lesions are centered behind the chiasm and stalk in the prepeduncular cistern. Although the ACoA/optic chiasm and pituitary stalk/gland are not necessarily the focus of surgery, they stand between the surgeon and the tumor, and therefore must be mobilized and safely "transposed" to get access to the tumor [11, 24]. Removal of the planum sphenoidale, tuberculum sellae, and bone over the entire anterior sella, as described for type I and II lesions, is needed. Additional inferior bony exposure is also required, extending into the sellar floor, to visualize the inferior intercavernous sinus (Fig. 23.6a, b). The superior intercavernous sinus is split, as previously described [24]. The dura is opened in a cruciate fashion based on the superior intercavernous sinus split [11], or a T-shaped incision is made from the chiasmatic cistern to the inferior intercavernous sinus [24]. The inferior intercavernous sinus is also split to control hemorrhage and increase access to the dorsum sella. The diaphragma is then opened and released from the infundibulum and pituitary. Dissection proceeds laterally around the pituitary gland, with release of adhesions to the medial walls

of both cavernous sinuses, and the gland is then free to be moved as needed to expose the dorsum sella and posterior clinoids. The bone of the dorsum and posterior clinoids is then removed with either a high-speed drill or ultrasonic bone aspirator, taking care not to damage the abducens nerve located inferolaterally [24]. Finally, the dura along the superior most part of the clivus can be opened and the tumor in the prepeduncular cistern accessed.

An "above and below" approach to the retroinfundibular area, prepeduncular cistern, and prepontine cistern has also been described, although this is not something we have done in our practice. The initial exposure for the "above" portion is as described above, although it is not necessary to expose the sella as inferiorly or to split the inferior intercavernous sinus. Dissection then proceeds through the suprasellar cistern, proceeding below the optic chiasm, superior to the pituitary gland, and lateral to the infundibulum. The working area lateral to the infundibulum and superior to the pituitary is used to access the retroinfundibular space and prepeduncular cistern. The "below" part of the exposure involves removal of the superior third of the clivus. The clival recess is identified below the sella, and bone removal proceeds caudally beginning at the level of the sellar floor. Bone removal is limited laterally by the carotid protuberances. The dura is then opened and the prepontine cistern accessed (Fig. 23.6c, d) [40]. The "above and below" approach and posterior clinoidectomy can be combined to address complicated tumors that require extensive exposure, but in our experience this is rarely indicated and may be better approached through staged procedures.

Angled endoscopes (30°, 45°, and 70°) are essential during the exposure and resection of retroinfundibular tumors to provide adequate visualization in all directions [11]. Resection begins with removal of exophytic portions and debulking, which creates the "wiggle room" necessary to initiate capsular dissection. Type III tumors usually adhere to the inferior hypothalamus and third ventricle, or the posterior infundibulum. These points of attachment must be identified and sharply dissected. Extracapsular dissection then proceeds posteriorly and inferiorly [24]. The capsule is sharply divided from the mammillary bodies, optic tracts, and the membrane of Liliquest [11]. The tumor can then be gently pulled forward from the basilar apex to expose the basilar artery and PCAs. Dissection then proceeds laterally with careful sharp release of the P_1 thalamoperforators at the posterior aspect of the capsule, and subsequent dissection along the oculomotor nerve [24].

Reconstruction

The complexity of reconstruction and the risk of CSF leak are determined by the type of EET approach and the tumor resected, although we generally feel that it is better to err on the side of more. Reconstruction for standard EET approaches to primarily sellar lesions is more straightforward, while reconstructing EET exposures with resection of a tumor extending into the third ventricle is more complicated with a high risk of CSF leak. For larger EET exposures, we combine a gasket

seal method with a fascia lata graft [41] and a nasal septal flap [11, 24, 41]. Fat grafts may be used to obliterate intracranial dead space and prevent CSF pooling, but are associated with increased risk of intracranial infection and obstructive hydrocephalus if overly generous [12]. We do not use intracranial fat grafts if the floor of the third ventricle has been opened.

A gasket seal closure first involves fashioning a piece of MEDPOR (Porex Corporation; Newman, GA) to the same size as the skull base defect. A fascia lata graft is cut to the dimensions of the skull base defect, with an additional approximately 1 cm overhang in every dimension, and this graft is delivered into the defect area. The MEDPOR buttress is then placed over the fascia lata graft and countersunk into the defect so that the buttress extends just beyond the bone edges and holds the construct in place [41].

After placing the gasket seal component, the nasoseptal flap is placed. A fat graft may be used to obliterate the sphenoid sinus prior to the placement of the nasoseptal flap. The nasoseptal is secured in place with DuraSeal (Covidien) or fibrin glue. This layer is then buttressed with a foley catheter balloon [24], nasal tampons [11], or other device.

Major Intraoperative Complication Avoidance and Management

Intraoperative complications are best avoided with careful preoperative planning and intraoperative technique, and, when they occur, they are addressed with the involvement of multidisciplinary team members as needed. Strategies for avoiding many complications, including postoperative CSF leak, approach related adverse events, and intraoperative neurovascular injury, have already been discussed and will not be reviewed here.

ICA injuries are one of the most feared, but thankfully rare, complications of EET surgery. Although the rate of ICA injury in EET procedures for craniopharyngioma is unclear, it occurs in approximately 0.2–2.0% of EET approaches for pituitary adenomas. ICA injury may be immediately apparent with significant intraoperative hemorrhage, or present days to years later with delayed epistaxis or pseudoaneurysm formation. Any patient with a suspected or an apparent ICA injury should undergo diagnostic angiography for further evaluation and possible endovascular treatment [42]. In the case of ICA injury with significant intraoperative hemorrhage, hemostasis must be obtained prior to transfer to the angiography suite. This is achieved with hemostatic agents and packing with cottonoids, augmented by a foley catheter balloon, nasal tampons, or other device if needed.

Endovascular sacrifice of the ICA remains the definitive management for ICA injury, particularly in the setting of uncontrolled hemorrhage. Sylvester et al. recommend a modified balloon test occlusion (BTO) prior to endovascular sacrifice, which entails angiographic evaluation of the collateral circulation with the balloon inflated and occluding the injured ICA, rather than neurologic assessment as the patient is usually under general anesthesia. However, endovascular sacrifice of the ICA can lead to significant neurologic deficits despite a reassuring modified BTO,

and endovascular repair techniques should be considered unless the patient is in extremis or is not a candidate for dual antiplatelet therapy. Dual antiplatelet therapy is required for stent graft or flow diverter placement. Some small series have shown encouraging results with endovascular repair of iatrogenic ICA injuries [42].

Severe morbidity and mortality can also result from intraoperative injury to neurologic structures, particularly the ON and hypothalamus. Once it occurs, there is little one can do to "manage" complications to these structures; therefore, the best strategy is to avoid injury. Approximately 75–93% of patients will have improvement in their vision after EET surgery [25, 26, 43–45], but some 2–7% of patients will have worsening [43–45]. Manipulation of the optic nerve should be minimized, and extreme care taken when dissecting tumor adherent to it. In our practice, we apply gentle retraction to the tumor and sharply dissect along the ON. Hyperphagia, significant weight gain, lethargy, and even coma can result from hypothalamic injury, which is especially severe in children [11]. In our practice, we always err on the side of accepting a subtotal resection rather than subjecting the patient to the risk of hypothalamic injury. We do not attempt to separate tumor from the wall of the third ventricle unless there is a clear plane that can be easily developed with minimal manipulation.

Postoperative Care

We admit all patients to the ICU or equivalent for close neurologic and hemodynamic monitoring following EET approach and craniopharyngioma resection. Patients with complex closure of large skull base defects typically require lumbar drainage for 24 h or longer to eliminate the risk of CSF leak and allow for "settling in" of the skull base repair. Rates of postoperative CSF leak were the historic "millstone hung around the necks" of endoscopic surgeons, with rates approaching 50% in some series; its successful management with CSF diversion, gasket seal closure and nasoseptal flap repair has helped to settle this issue, but serves to emphasize the importance of this multipronged approach to complication avoidance [10, 21, 24–26, 43–45]. If a postoperative CSF leak persists, it should be managed conservatively with continued temporary CSF diversion, head of bed elevation, and a bowel regimen [35]. Permanent CSF diversion may be a reasonable next step in some cases that persist despite conservative management [24]. EET reexploration or craniotomy may be necessary in certain cases, although this has never happened to us (yet).

Diabetes insipidus should be expected and its management anticipated after this surgery [43–45], but will usually resolve over about a month [45]. Careful monitoring of sodium, urine specific gravity, and fluid status is important. Diabetes insipidus is effectively managed with free water replacement and vasopressin. Anterior pituitary dysfunction will be present in 38–57% of patients [43–45]. Stress dose methylprednisolone should be continued in the immediate postoperative period [11]. Careful endocrine monitoring in collaboration with an endocrinology team is important. In patient with documented preoperative HPA axis deficiency stress dose hydrocortisone should be given intraoperatively followed by a quick taper to physiologic dose.

We usually continue with GC replacement till 3 months and then reassess with morning cortisol and cosyntropin stimulation test. In patients with intact HPA axis preoperative, a post op day one cortisol of >14 ug/dl indicates intact adrenal function [46]. The need for thyroid replacement is typically assessed 10–14 days after surgery. Gonadal and growth hormone are assessed and replaced after 3 months of surgery. The decision of replacement with the hormones varies on a case-by-case basis.

Proper postoperative nasal care is important for healing of the skull base reconstruction. Gentle debridement of the nasal cavity should begin about 1 week after surgery, and involves removal of crusting, dried blood, and the breakdown products of hemostatic agents. The skull base should be inspected to ensure expected healing. As more time passes and the risk of causing a CSF leak decreases, debridement can become more aggressive. Most patients have complete healing of their reconstruction about 6–12 weeks after surgery [35].

Acknowledgments The authors would like to thank Dr. Mahlon Johnson for providing us with representative pathologic photomicrographs.

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Transsphenoidal Surgery for Cushing's Disease

24

Kalmon D. Post, Margaret Pain, Hekmat Zarzour, and Joshua Bederson

Preoperative Evaluation

The first-line treatment of Cushing's disease is surgical resection [1, 3, 5, 6, 19, 21, 24, 26, 33, 34, 38, 39]. All patients with clinical evidence of Cushing's disease should receive a full work-up to determine the source of the hypercortisolemia. Referral to a neurosurgeon is only necessary if the source of the endocrinopathy is suspected to be the pituitary gland. However, we believe that neurosurgeons operating on patients with Cushing's disease must understand the preoperative work-up and be secure in the results along with the endocrine team. Mistakes in diagnosis are a frequent event when dealing with these patients. We will not review all the endocrine testing here.

MRI is used to locate the tumor within the sella turcica (Fig. 24.1). In comparison to other pituitary tumors, ACTH-secreting adenomas tend to be smaller in size and often located in the midline [2]. Standard MRI may detect larger tumors, but when it fails to do so, higher field strength or different views can be done to maximize the sensitivity of the study. Significantly more sensitive detection of pituitary microadenomas is possible with 3 T MRI (P <0.016) than 1.5 T MRI. However, no difference was reported between 3 T and the 3 T o-CRH examinations [8]. Spoiled gradient recalled acquisition in the steady state has higher sensitivity (80%; confidence interval, 68–91 vs. 49%; confidence interval, 34–63%), with higher

K.D. Post, MD (✉)
Department Neurosurgery, Mount Sinai School of Medicine, Mount Sinai Health System, New York, NY, USA
e-mail: kalmon.post@mountsinai.org

M. Pain, MD • J. Bederson, MD
Department of Neurosurgery, Mount Sinai School of Medicine, New York, NY, USA

H. Zarzour, MD
Department of Neurosurgery, Jefferson University Hospital, Philadelphia, PA, USA

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_24

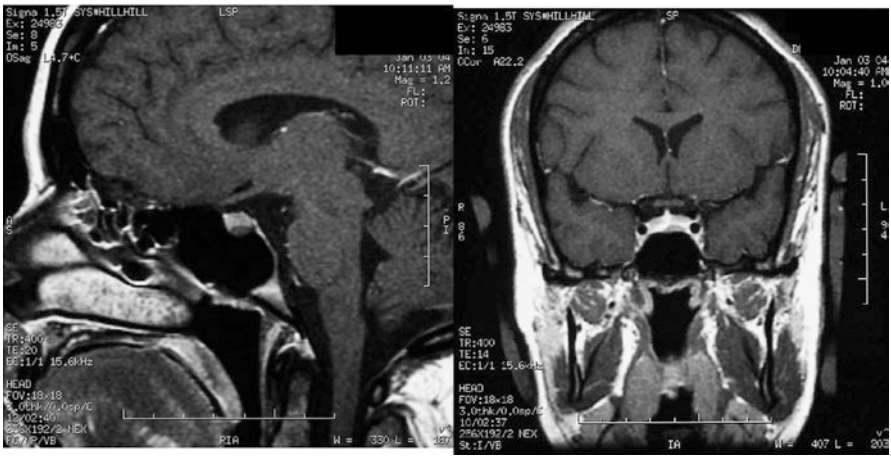

Fig. 24.1 1.5 T MRI brain T1 postcontrast in sagittal and coronal views demonstrating mass in the left inferior sella turcica; note that tumors demonstrate delayed enhancement relative to the normal gland

false-positive rate (2 vs. 4%) compared with standard T1-weighted spin echo [35] in detection of ACTH-secreting pituitary tumors. However, the MRI must be interpreted with care as incorrect lateralization can occur as well as identification of a tumor that is not the source of the ACTH secretion [22, 36].

ACTH-secreting microadenomas, are not detectable in 40–50% of the patients [43]. In such cases IPSS (inferior petrosal sinus sampling) can be helpful in confirming the pituitary gland as the source of the ACTH secretion (see below). The indication for transsphenoidal surgery of the pituitary gland is then based only on biochemical data indicating the origin of hypercortisolism to be the sella [17, 49].

In addition to tumor detection, MRI provides valuable information for the surgeon to assess surrounding structural anatomy. In particular, compression or invasion of the cavernous sinus occurs with larger tumors. Sol et al. [41] retrospectively studied 63 patients who had undergone surgery and compared the preoperative MRI with intraoperative findings for cavernous sinus invasion. If T1 sequence with contrast did not show periarterial enhancement, invasion is highly probable (positive predictive value, 86%; P <0.001). In the same study, no medial wall of cavernous sinus on T2 sequence and the lesion crossing lateral to the inner carotid line revealed invasion in 87.5% and 85% respectively [41].

CT is rarely used for localization of the adenoma but can aid in operative planning. As modern navigation equipment utilizes bony anatomy for surgical planning, high resolution CT is the preferred imaging modality for this technology. Improper localization of the midline of the anterior sella wall can result in high risk of injury to the patient. For example, a lateral, rather than a midline, opening of the anterior wall of the sella exposes the cavernous sinus, cranial nerves, and carotid artery to possible injury [9]. In addition to a higher risk of complications, the risk that the surgeon may not be able to access the tumor is also increased.

If endocrinological studies are diagnostic of Cushing's disease, and imaging studies are negative for any definitive pathology, further tests should be performed to confirm the diagnosis of Cushing's disease before surgery.

Inferior petrosal sinus sampling (IPSS) can be used to corroborate a pituitary source for ACTH hypersecretion [17, 49] (Fig. 24.2). IPSS is indicated to exclude extrasellar ectopic ACTH secretion and to suggest the laterality of the tumor within the sella turcica (Table 24.1). Access to both inferior petrosal sinuses is achieved

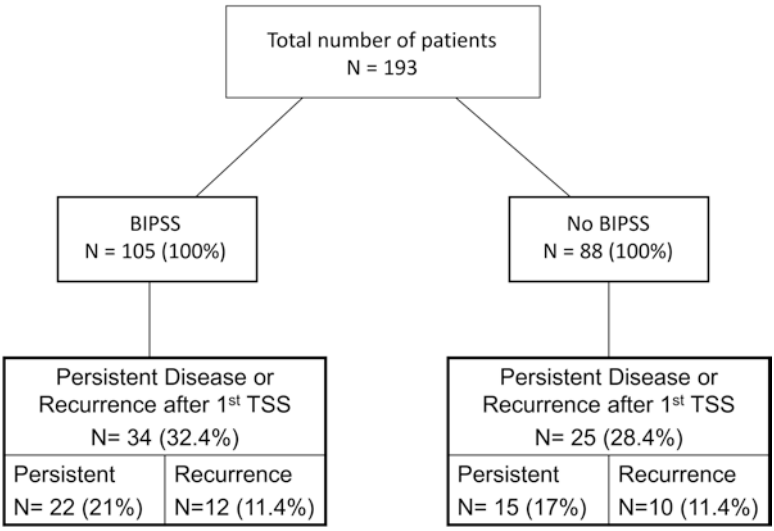

Fig. 24.2 Results of transsphenoidal surgery for Cushing's disease with or without preoperative inferior petrosal sinus sampling (Jehle et al. [17])

Table 24.1 Summary of indications and findings for inferior petrosal sinus sampling in the diagnosis of Cushing's disease

Indications and findings of inferior petrosal sinus sampling
Indications:
With clinical suspicion of Cushing's disease and negative radiological studies
To help localize the tumor after previous unsuccessful pituitary surgery
To help determine the likelihood of pituitary adenoma versus ectopic ACTH production in indeterminate cases
Findings:
Measurements of ACTH taken from bilateral inferior petrosal sinuses at baseline and then fixed intervals after CRH stimulation
Baseline gradient of 2:1 central to peripheral hormone concentration localizes the source of ACTH to the sella
Gradient between the inferior petrosal sinuses determines likely laterality (rate of false/failed lateralization ~30%)
Gradient of >3:1 central to peripheral hormone after CRH stimulation suggests source of ACTH is from the pituitary

with endovascular catheters directed at each side via the femoral veins. Baseline sampling of ACTH is performed and then compared with the local concentration produced in each sinus after CRH stimulation. While the study can help to suggest the gross laterality of the tumor, the results can be compromised by several factors. Improper catheterization of the inferior petrosal sinus, alternate flow of the sinus into the cavernous sinus, and anomalous venous drainage can all lead to false lateralization. Generally, the study has higher sensitivity and specificity for identifying the cause of hypercortisolism (80–100% sensitivity, greater than 95% specificity) [12]. This test might help guide the surgeon intraoperatively in cases where no distinct tumor is found during operative exploration. However, the IPSS correctly predicted the side of the pituitary gland that contained the tumor only in 69%, whereas the tumor was located contralaterally in 31% [47]. The IPSS is an invasive study and carries certain risks. Among the more common complications noted are tinnitus and otalgia (1–2%) and groin swelling and hematoma (2–3%) [12]. Rarely, 1.5%, more serious complications have been reported, including, but not limited to nerve palsy, SAH, and brainstem infarction [10] (Fig. 24.3). IPSS is also indicated in postoperative cases when no tumor was found within the sella but the patient continues to demonstrate hypercortisolism and IPSS had not been done preoperatively. Positive IPSS in these cases might be suggestive of a pituitary adenoma with an abnormal location such as the cavernous sinus or pituitary stalk but could just confirm adenomas that were missed during surgery. It lends support for re-exploration [31, 37, 46].

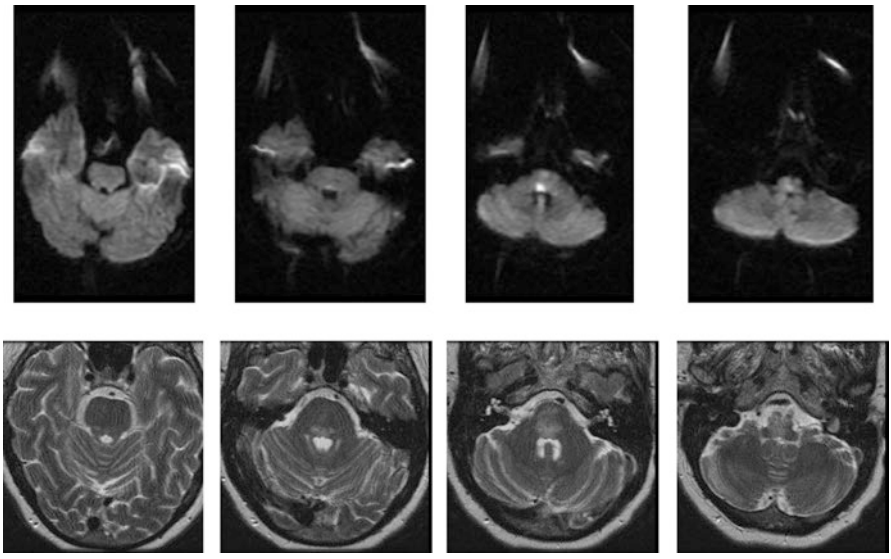

Fig. 24.3 MRI brain, axial sections, diffusion weighted (**top**) and T2 weighted (**bottom**) demonstrating post-IPSS brainstem stroke

Decision for Surgery

If surgery has not been performed, this is clearly our first choice for therapy. It has the highest potential for remission in experienced hands. If surgery has already been done and unsuccessful in leading to remission, then there are several options. If an ACTH-secreting adenoma has been resected and confirmed pathologically, we will most often opt for re-exploration and a more aggressive resection. If surgery was based upon an abnormal interpretation of the MRI and an adenoma has not been found, then we will perform an IPSS study to confirm the pituitary etiology if this was not performed previously. If positive, then re-exploration is done. If negative, then further work-up is required to identify the true etiology.

Surgical Indications

As ACTH-secreting adenomas tend to be microadenomas, the primary goal of most surgical interventions is relief of the underlying endocrinopathy. Less frequently, surgery is performed to reduce mass effect of the tumor on surrounding structures. Rarely, surgery is done to confirm a diagnosis of Cushing's disease when there is high suspicion from all endocrine data, the MRI is negative, and the patient is suffering significantly. Macroadenomas account for a few ACTH-secreting tumors. Most series report 5–9% of tumors to be greater than 1 cm in maximal diameter [4, 6, 13, 15]. These lesions are remarkable as most lesions become symptomatic due to endocrine hypersecretion while still small in size. These systemic effects of hypercortisolism are observed in more than half of the patients affected and include centripetal obesity, hypertension, hypercholesterolemia, hirsutism, and psychological difficulties, less diabetes mellitus, osteoporosis, "moon" facies, myopathy, menstrual irregularities, atherosclerosis, headache, and dermatologic abnormalities [27]. In some patients who have diabetes and/or hypertension that are difficult to control, the anesthesia risk may be improved with preoperative medical therapy to control the cortisol levels allowing better control of blood pressure and glucose levels. There are numerous medications available now, but we most commonly use ketoconazole in this setting.

Preoperative Difficulties for Cushing's Disease

Undetectable adenoma on preoperative MRI and invasive adenomas are two of the main challenges in Cushing's disease. The remission rate for microadenomas that are detected on preoperative MRI is very high [36, 43]. It is well known that remission rates are lower with negative MRI cases [17, 37, 47, 49]. Finding the adenoma in these cases is not easy. Adenoma invasion presents another surgical challenge for Cushing's disease [28]. When the cavernous sinus and surrounding structures are invaded by the tumor, total adenoma resection may be impossible and dangerous to attempt [28]. Remission rates are lower for invasive tumors compared with those where a complete resection can be achieved [18, 38, 50]. The likelihood of invasion

increases with tumor size and so while larger tumors may be more easily identified, a total resection can still be difficult. Adenomas associated with dural invasion tend to be larger (2–37 mm) compared to noninvasive tumors (2.5–12 mm) [25]. Unfortunately, dural invasion is not well characterized by preoperative imaging and tends to underestimate the prevalence of invasive tumors (22% of cases). This is compared with an estimated 34% of patients who had histologically confirmed dural invasion [25]. If the invasion is limited to the dural medial wall and does not penetrate the cavernous sinus, complete resection is probably achievable with a high rate of remission [25, 26, 30]. However, once the medial wall of the cavernous sinus is breached, surgical remission is unlikely and additional treatment is frequently required [30]. However, with endoscopic techniques medial cavernous sinus tumor may be seen and resected.

Surgical Techniques

Routine antibiotics are given prior to surgery and postoperatively until nasal packing has been removed. Perioperative steroids are not given as they may affect the postoperative testing. Also they are unnecessary as this group of patients is hypercortisolemic and will not have stress difficulty.

We use navigation or C-arm fluoroscopy depending on the anatomical situation. In reoperations we prefer to have navigation. We always prepare the abdomen for a possible fat graft.

The techniques are virtually the same whether a microscopic or endoscopic technique is used. For a microscopic approach, we generally use the right nostril with the patient in the supine position, head tilted to the left, and slightly turned to the right. However, if the adenoma is seen on imaging and is located in the right lateral wing of the gland and sella, the left nostril may give better advantage as there is always some deviation to the opposite side during a microscopic transnasal approach. With an endoscopic technique, we use a binostral technique, and often with an ENT surgeon, as this is more of a four-handed procedure. Fluoroscopy or intraoperative navigation tools confirm the trajectory to the sphenoid sinus and sella (Fig. 24.4). However, the most important trajectory is the midline. With navigation, this is assured. With fluoroscopy, the vomer must be well exposed and is virtually always midline. Septations in the sphenoid sinus cannot be utilized for midline identification and often lead to the carotid canal (see Fig. 24.4).

Using endoscope or microscope, a broad exposure of the sella and pituitary gland is required to allow visualization of the entire anterior lobe. Exposure of the anterior sella wall is complete when the faint blue edge of the cavernous sinus can be visualized on either side of the field. Various incisions of the dura are used but we prefer an «H» opening. Cruciate or box incisions are also used. There is often a large venous sinus between the cavernous sinuses, both superiorly and inferiorly, that can lead to rapid bleeding when opening the dura. A variety of techniques can be used to stop the bleeding, but it often restarts when manipulating the gland and dissecting it away from the dura. Patience and the use of surgifoam, surgicel, and cautery are

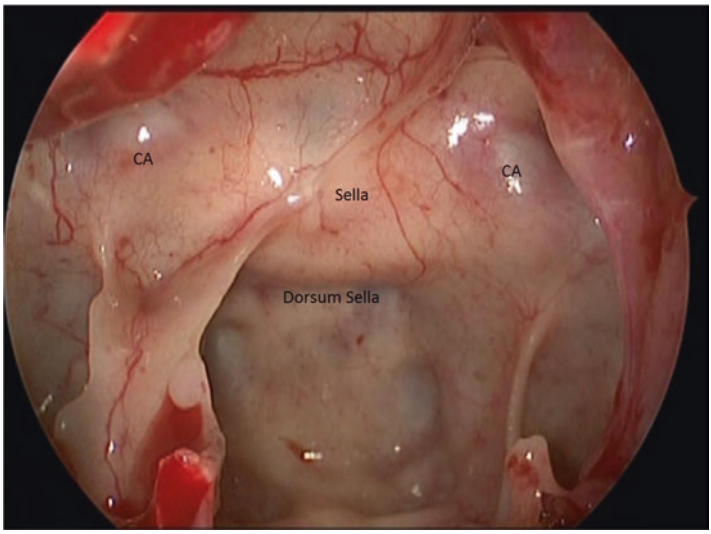

Fig. 24.4 Transnasal transsphenoidal endoscopic view of sella turcica; note the septation of the sphenoid sinus courses diagonally relative to midline; *CA* carotid artery

all useful, but it must be stopped as otherwise visualization of the gland and adenoma will be difficult if not impossible.

Few studies describe and report outcomes of pituitary surgery that focus on the method for adenoma removal once the sella has been opened, but this is the critical portion of the operation [20, 29, 32]. The anterior pituitary gland has its own thin capsule that separates it from the surrounding dura, sella, and cavernous sinus, and it has a collagen matrix which gives it a firm texture and allows it to be distinguished from the adenoma which tends to have a soft consistency and different color. As an adenoma grows, it causes compression of the normal pituitary tissue and forms a pseudocapsule [32]. Careful dissection within the pseudocapsule, using it as the surgical plane is the key for total and successful resection. Appreciation of the pseudocapsule is important to ensure gross total resection, as well as to diagnose dural invasion. However, finding the adenoma is not always easy.

After dural incision, the surface of the anterior gland is carefully inspected for areas of irregularity or discoloration. Some authors have reported the use of a micro-Doppler for visualization with varying degrees of success [45].

Separating the gland from the dura with fine dissectors will often demonstrate a soft area suggesting the adenoma. Often there will be no hint on the external surface of the gland. If the MRI has demonstrated the adenoma, then sectioning into the gland at that site is carried out. The visualization of the pseudocapsule is the most important finding to locate the tumor. Once the possible location of the adenoma is identified, the pituitary capsule is incised sharply and then the pseudocapsule is dissected. We try to avoid piecemeal resection, when possible. Special care is taken not to lose any of the specimens in the suction.

Sectioning of the gland is performed if no adenoma can be detected after gross inspection of the anterior and lateral surfaces and the MRI did not demonstrate the adenoma. Incisions are made horizontally or vertically at 2 mm intervals until a tumor is uncovered or the posterior gland is identified. The sectioning can be directed somewhat by lateralization on IPSS studies, but it is known that this may only be 60% accurate. If the adenoma is uncovered, then dissection of the pseudocapsule is performed with attempted gross total resection. If the pseudocapsule or surrounding dura is breached, careful inspection is performed to ensure that no areas of dural invasion are missed. Jagannathan et al. [16] determined the success of using the pseudocapsule as a surgical capsule through a retrospective review of 261 patients. Tumor was identified radiographically in only 135 patients (52%). However, through meticulous exploration of the sella and identification of the pseudocapsule, the group was able to attain remission in 252 cases (97%).

If no tumor can be identified, endocrinological remission is still possible but benefits from a thorough re-evaluation of the patient's circumstances. A partial or total hypophysectomy can be considered [40]. Persistent disease almost always results from recurrent or persistent tumor [7]. However, if the tumor cannot be located on further workup and on reoperation, other surgical alternatives may be necessary. Hypophysectomy affords the maximum opportunity for removal of cryptic tumors but carries additional morbidity. Because panhypopituitarism develops after total resection of the pituitary, a partial resection is preferred and can be directed based on the results of the preoperative IPSS. With partial hypophysectomy, a high rate of remission can be achieved [26].

Depending on the clinical situation, more aggressive or more conservative resection may be indicated. For the seriously debilitated or elderly patient, transsphenoidal surgery may be attempted first but if no adenoma is found, it may be appropriate to perform complete hypophysectomy to minimize the need for repeated surgery. With tumors invading the cavernous sinus, there is a definite advantage to endoscopic techniques. With an angled scope, the medial wall of the cavernous sinus is well seen and can be opened. Tumor medial to the carotid artery can be removed. However, adenomas with a Knosp grade of 3 or 4 cannot be completely and safely removed [23].

After completing resection of the adenoma, we routinely inspect for possible CSF leak with a Valsalva maneuver. Any evidence of communication of cerebrospinal fluid with the sella mandates compulsive intrasellar closure. Closure of the surgical site is accomplished by placing a piece of fat within the sella, followed by a piece of the vomer taken during the approach to repair the broached anterior sellar wall. If no bone is available, we use a biodegradable substitute. If no CSF is seen, we still close the bony wall as above, but often without fat. In patients with CSF seen, we also often pack the back of the sphenoid sinus with fat as well. During endoscopic procedures, we tend to use a mucosal flap to close the posterior wall of the sinus. This closure for the typical ACTH adenoma is more limited than that necessary for extended transsphenoidal openings for other tumors. We do not use spinal drains.

If a microscopic technique was used, a unilateral nasal tampon is placed and maintained for the first 2 d after surgery. In some patients, particularly Cushing's disease cases, bilateral nasal tampons are needed because of the oozing.

With endoscopic cases, internal packing alone may be adequate as there may not be a mucosal flap.

In the perioperative period, antibiotics are administered but no steroids. Our goal is to test serum cortisol and ACTH levels the next morning to determine the success of the surgery.

Endoscopic Versus Microscopic

Both the surgical microscope and endoscope techniques have been used to access the sella through a transsphenoidal approach (Table 24.2). Microscopic surgery has been considered to be the standard of care for many years, and in experienced hands it is associated with minimal morbidity and mortality. With advancements in optics and operator experience in endoscopy, this method has become increasingly popular. Endoscopy offers two main advantages in surgery of the sella: improved visualization of the entire surgical field and the ability to make an extended opening of the skull base. However, most endoscopes only project a two-dimensional image and therefore lack the depth perception afforded by the operating microscope.

In their review of 61 cases of Cushing's disease treated with endoscopic surgery, Starke, et al. found that this method was a safe and effective means of resolving hypercortisolemia [42]. Gao et al. in 2014 [11] performed a systematic review comparing the results of endoscopic to microscopic surgery. Their search of all articles published after 1992 included a total of 15 studies and 1014 patients. They found a higher rate of gross total resection and lower rate of septal perforation in the endoscopy group but no significant difference in the rate of complication or length of surgery. They concluded that the endoscopic transsphenoidal approach is safer and more effective than microscopic surgery. Higgans et al. [14] retrospectively analyzed 19 and 29 subjects who had undergone endoscopic excision and microscopic excision respectively. They analyzed demographics, tumor characteristics, operative details, length of hospital stay, intraoperative and postoperative complications, level of postoperative pain, recurrence rate, use of computed tomography (CT) image guidance, and length of follow-up. They concluded that the two techniques have similar intraoperative characteristics and immediate complication rates.

Table 24.2 Comparison of advantages and disadvantages of microscopic and endoscopic approaches to the sella

Technique	Advantages	Disadvantages
Microscopic	Less setup allows for potential for shorter operative times Low morbidity/mortality Views in three dimensions allows better depth perception	Smaller field of view Not able to access the cavernous sinus
Endoscopic	Increased field of view through multiple types of scopes Allows potential for extended approach to the skull base	Typically two-dimensional images are projected Requires two surgeons

Tumors in the cavernous sinus are generally not accessible by the microscopic surgical approach and adjuvant therapy is usually required [25, 30]. But, as noted above, endoscopic approaches may allow resection of Knosp grade 2 tumors [48].

Post-op

Postoperatively we observe the patient very closely for possible Addisonian symptoms as we do not use perioperative cortisol replacement. No intraoperative steroids are used so as not to suppress postoperative levels. This requires a patient unit very accustomed to such patients or an ICU setting. We do not use the ICU for this unless the patient is very labile in blood pressure or glucose control. We measure cortisol and ACTH the two mornings following surgery. If there is adequate reduction of these, we begin hydrocortisone replacement immediately and discharge on suprareplacement doses. If levels remain very elevated, we will observe over a longer period of time before deciding if there is any suggestion of disease control [44]. If eucortisolemic postoperatively, we start hydrocortisone replacement as there is concern for relative insufficiency and possible further reduction of cortisol levels to true insufficiency.

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Transsphenoidal Surgery for Acromegaly

25

Edward R. Laws, Jr., David J. Cote, and Sherry Iuliano

Introduction

In some respects, acromegaly is one of the most straightforward problems associated with hyperfunctioning pituitary adenomas. Acromegaly is a devastating disease with multiple comorbidities affecting many systems, and is associated with shortening of the lifespan if uncorrected [1–5]. At the present time, most patients with growth hormone–secreting pituitary adenomas are candidates for surgery as first-line therapy [6, 7]. Medical management of acromegaly continues to improve, however, and currently is a useful adjunct [2, 8]. Radiation therapy has been utilized in the past, but is less commonly necessary now, as control from medical treatment and surgery has become progressively more efficient [9].

Among the pituitary adenomas, growth hormone–secreting lesions represent approximately 20% [1, 2, 10, 11]. Often, acromegaly can be a subtle disease, and many patients, in retrospect, have been suffering from the effects of elevated growth hormone for 5–20 years prior to the ultimate diagnosis. This delay in diagnosis allows the comorbidities of the illness to develop over time, complicating the patients' general health status. Common comorbidities include hypertension, cardiovascular disease, cerebrovascular disease, diabetes mellitus, arthropathies, carpal tunnel syndrome, sleep apnea, snoring, hyperhidrosis, malocclusion and gapping of the teeth, and enlargement of the jaw [1, 12, 13]. In the case of macroadenomas associated with acromegaly, patients may suffer visual impairment from compression of the optic chiasm, and progressive hypopituitarism from compression of the normal pituitary gland. Many patients with acromegaly have a predisposition to vascular disease, including enlargement of and atherosclerotic and dolichoectatic changes in the vessels of the intracranial circulation (Fig. 25.1).

E.R. Laws, Jr., MD, FACS, FAANS (✉) • D.J. Cote, BS • S. Iuliano, MSN, NP-C
Department of Neurosurgery, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA
e-mail: elaws@partners.org

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_25

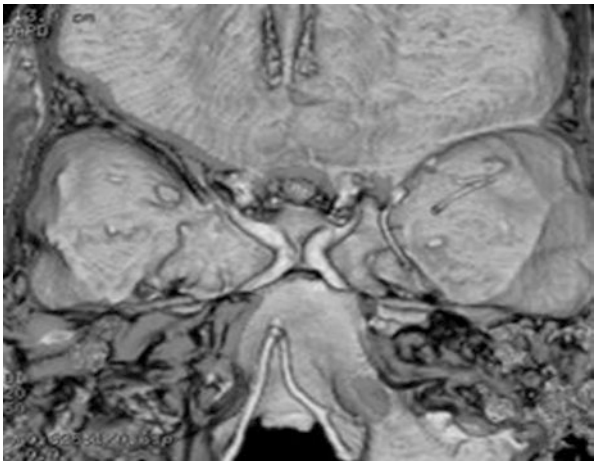

Fig. 25.1 Preoperative CTA showing enlargement and abnormal anatomy of the bilateral cavernous carotid arteries in a patient with active acromegaly

Diagnostic Aspects

Once suspected, the diagnosis of acromegaly can be made using laboratory tests. An elevated IGF1 is an essential characteristic of acromegaly, and is the primary means of making the endocrine diagnosis [2]. Acromegalic patients will also have an elevation of growth hormone levels, and may have an elevation in prolactin as well, as the same stem cell produces growth hormone and prolactin [14]. Approximately 30% of the surgical specimens in patients with acromegaly will stain immunocytochemically for both growth hormone and prolactin [13, 15–17]. It is important to measure the other related pituitary hormones, including cortisol, thyroid hormone, TSH, and gonadotropins (testosterone in men, and LH and FSH in women), as these can be affected by the growth of the tumor. Occasionally, patients with large tumors will develop disorders of fluid and electrolyte balance and may have diabetes insipidus or SIADH at presentation.

The anatomic diagnosis and staging is ordinarily made using MRI (Fig. 25.2). These imaging studies demonstrate the size and conformation of the tumor, whether there is invasion of the cavernous sinuses, whether there is suprasellar extension affecting the optic chiasm, or whether there is erosion of the floor of the sella and projection of the tumor into the sphenoid sinus [18].

Patients who present with visual symptoms should be evaluated by a neuro-ophthalmologist. Visual acuity studies and visual field examinations are mandatory, and these may be supplemented by optical coherence tomography (OCT) to evaluate the thickness of the retinal nerve fiber layer, which may reflect compression of, or damage to, the optic apparatus [19, 20].

Once the diagnosis has been made, the patient must be evaluated for suitable therapy. The advantage of surgical removal of the tumor is that the growth hormone levels fall immediately toward normal [2, 10, 14, 21]. IGF-1 levels fall slowly, and it may be 2–3 months before a postoperative nadir is reached [14]. Medical therapy

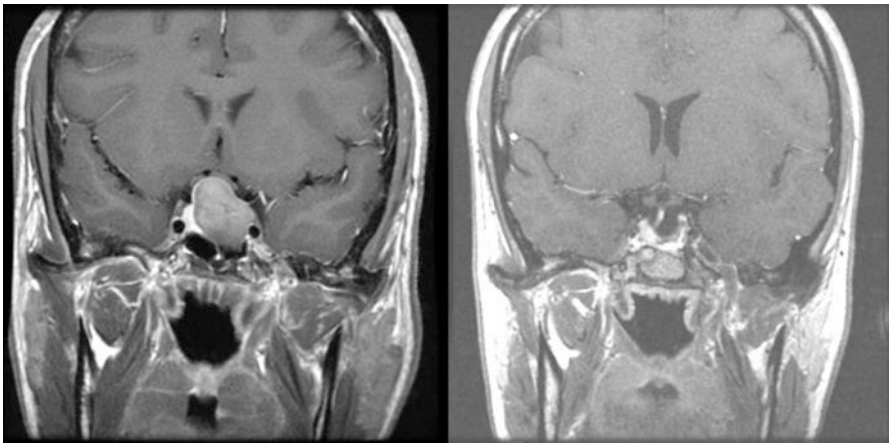

Fig. 25.2 Preoperative (*left*) and postoperative (*right*) coronal MRI scans for a patient undergoing endoscopic transsphenoidal surgery for acromegaly

can be considered for some patients who are not surgical candidates, or older patients who have very mild evidence of disease [8]. In some cases it might be prudent to pretreat medically in order to make the patient a better candidate for surgery and anesthesia. Current choices for medical therapy include cabergoline (most useful in patients who have tumors that co-secrete prolactin), somatostatin analogs, and growth hormone receptor blockers. These agents may be used individually or in combination, and have the potential of controlling excess growth hormone secretion in more than half of the patients with active acromegaly [2].

When surgery is considered, a number of preoperative concerns and anesthetic issues should be addressed. Hypertension, when present, should be adequately treated, and the cardiac status should be carefully investigated, particularly for evidence of cardiomyopathy. Patients with sleep apnea likewise should be evaluated and treated when necessary. Many patients with acromegaly have hyperlipidemia and this too should be evaluated and treated.

Anesthetic precautions for surgery include arterial pressure monitoring, and the anticipation of endotracheal intubation difficulties, with intubation often requiring awake fiberoptic intubation techniques [22]. In our practice, we rarely use a lumbar intrathecal drain for normal pituitary tumor cases. The preoperative fasting cortisol level determines whether or not the patient receives corticosteroids during surgery. In general, if the fasting serum cortisol is less than 10 ng/L we provide cortisol support during the operation and the immediate recovery period. If thyroid function is impaired preoperatively, thyroid repletion is instituted. When this is done in patients with borderline cortisol levels it is another indication for cortisol support during surgery, as the thyroid hormone related increase in metabolism can result in a demand for higher cortisol levels [21, 23]. It is also wise to be sure that the serum calcium levels are normal as the rare patient with acromegaly may have the MEN-1 syndrome with undiagnosed parathyroid involvement [24]. Our experience in these areas recently led to the

development of a transsphenoidal surgery checklist, adapted in part here in Tables 25.1, 25.2, and 25.3 [22]. This checklist includes both preoperative anesthetic concerns and intraoperative considerations to improve patient outcomes.

Table 25.1 Anesthesia pause: transsphenoidal surgery checklist

	ANESTHESIA PAUSE
Patient Identification	
□	Name
□	Hospital Record Number
□	Allergies
Diagnoses	
□	Surgical Diagnosis
□	Anesthesia Concerns (Airway classification, Cushing's/Acromegaly, Diabetes, Hypertension, Cardiovascular/Pulmonary)
□	Pertinent Labs (Cortisol, T4, CBC, Coags)?
Medications	
□	Antibiotics
□	Corticosteroids
□	Insulin
□	Avoid Decadron for nausea
Surgical Preparation	
□	Pre-operative nasal decongestant spray
□	Nasal Pledgets--cocaine, lidocaine, epinephrine
Positioning, Airway, and Access	
□	Mayfield or Horseshoe headrest in place
□	Image Guidance (if available)
□	ET tube fixated to left corner of the mouth and jaw
□	Avoid tape on upper lip
□	Thorax elevated
□	Eye protection in place
□	Orogastric tube in place
□	Pad and tuck right arm
□	Avoid BP cuff on right arm, if possible
□	TEDS or pneumatic boots on legs
□	Patient prepped for potenital graft (fat and/or fascia lata)
Fluid Management	
□	Careful I/O
□	DI present or anticipated
Monitoring	
□	Central/Arterial line (usually not necessary)
□	Urinary Catheter (often not necessary)
Special Considerations	
□	Patient protocolled for blood and tissue samples to pathology

Adapted from Laws et al., *JNS* (2015)

Table 25.2 Surgical and equipment pauses: transsphenoidal surgery checklist

	SURGICAL PAUSE		**EQUIPMENT PAUSE**
Team Identification		*Microscope*	
□	Personnel introductions (anesthesia, nursing, scrub, techs, surgeons, other)	□	Set up and balanced, with observer head on the left
Operative Procedures Planned		*Endoscopes*	
□	Operation type (initial or recurrent)	□	Light source ready
□	Tissue grafts anticipated (fat, fascia lata)	□	Monitors
□	Nasal septal flap anticipated	□	Camera/Video
□	Lumbar intrathecal drain anticipated		
□	Estimated duration of surgery	*Image Guidance*	
		□	Stealth/Stryker/Brainlab/etc.
Blood			
□	Anticipated blood loss		
□	Type and crossmatch, units requested	*Electrocautery*	
□	Coagulation state	□	Suction Monopolar, Pistol Grip Biopolar
		□	Suctions
□	Special issues (e.g., Jehovah's witness)	□	Colorado tips
Specimens Anticipated		*Other*	
□	Cultures	□	Microdebrider
□	Tissue Specimens (frozen and standard)	□	Ultrasonic microdoppler
□	Research specimens	□	High speed drill (diamond bits)
		□	Additional Equipment
□	Questions or concerns from anyone on team		

Adapted from Laws et al., *JNS* (2015)

Table 25.3 Closure pause: transsphenoidal surgery checklist

	CLOSURE PAUSE
Post-Operative Destination	
□	Disposition (ICU, Floor)
□	Nasal Packing
□	Steroid Management

Adapted from Laws et al., *JNS* (2015)

Surgical Considerations

The goals of surgery for the treatment of pituitary adenomas associated with acromegaly consist of normalization of growth hormone and growth hormone dynamics (GH levels during an oral glucose tolerance test) [2], removal of mass effect and decompression of the optic chiasm, preservation or restoration of normal pituitary function, and avoidance of a postoperative spinal fluid leak [16, 25].

Except for unusual situations, the preferred surgical route of access for pituitary tumors is by the transnasal, transsphenoidal pathway. This can be done with either the operating microscope or the operating endoscope, each of which has relative advantages and disadvantages [10, 15]. Over the past 8 years, 93.5% of our operations were undertaken using the operating endoscope. In general, we begin with the operating endoscope, and occasionally employ the microscope in cases where the nasal mucosa is particularly thickened or intraoperative bleeding is excessive, inhibiting safe and effective use of the endoscope. During endoscopic surgery, as in all neurosurgery, patient positioning is critical. Our center uses a two-surgeon technique with the patient's head angled (Fig. 25.3). Craniotomy is generally reserved for very large tumors that are eccentrically located and have major extensions in the suprasellar space. Normally we prefer the fronto-orbital craniotomy approach with splitting of the Sylvian fissure. On rare occasions a combined craniotomy/transsphenoidal approach may be indicated [26, 27].

Even though patients with acromegaly often have large noses and wide alar apertures, the transnasal approach can be difficult [28]. In general, the nasal mucous membranes in patients with acromegaly are engorged, thickened, and highly vascular. There may be significant polyposis along the nasal pathway, and there may be a septal deviation or septal spurs that complicate the exposure. It is

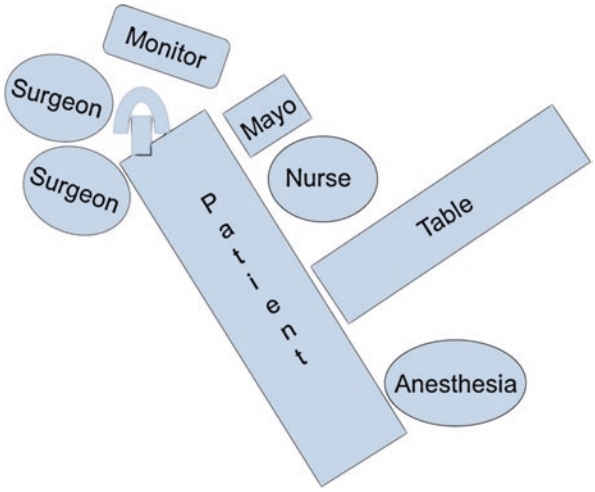

Fig. 25.3 Patient positioning for endoscopic transsphenoidal surgery for acromegaly

important to deal with these effectively. The hypertrophy of the mucosa may occlude visualization of the sphenoid ostia, and image guidance is often helpful. In acromegaly, the bone is stout and vascular, and may require stronger instruments than usual. The vomer, in particular, may represent a significant obstacle and may need to be drilled or chiseled away in order to gain sufficient exposure. Careful dissection of the posterior mucosal flaps is important, with preservation of, and care to prevent injury to, the sphenopalatine arteries on either side. Although the sphenoid is usually large and well aerated, there may be significant stout septal bony compartments within the sphenoid sinus, as well [18]. The surgical approach, and sometimes the operative field itself, are usually monitored using image guidance, so that the midline of the field is clearly seen, along with tuberculum of the sella superiorly and the clivus below. When the dura is exposed, the ultrasonic Doppler probe can be utilized to confirm the position of the carotid arteries and to be certain they are free from harm when the dura is opened [29]. A wide exposure is preferred in nearly every case, from one cavernous sinus to the other, and from the tuberculum to the floor of the sella.

Although the pituitary tumors in acromegaly may occasionally be invasive of the floor of the sella and the cavernous sinuses, the substance of these tumors is usually quite soft and readily removed with suction. Often there is a clear demarcation between the tumor and the surrounding normal gland. Even with pseudoencapsulated tumors, however, it may be wise to try to remove a thin margin of the normal gland adjacent to the obvious tumor. When the tumor extends into the cavernous sinuses, there may be significant venous bleeding as the tumor is resected from within the sinus. When gross evidence of dural invasion is present, every attempt should be made to resect the involved dura when possible [10]. If removal of the tumor results in spinal fluid leak, it is our practice to repair this with an abdominal fat graft carefully tailored to fill the sella, and secured in place with a carefully tailored piece of cartilage, bone, or an artificial plate. We rarely use sealants or glue, and do not ordinarily pack the sphenoid sinus. At the completion of the procedure, the field is carefully inspected for excellent hemostasis, the middle turbinates are slightly medialized, and the nasal septum put into midline position, usually without any packing of the nose.

In order to illustrate the presenting demographics, comorbidities, surgical approach, pathologic phenotypes, and complications associated with treatment of acromegaly in a high-volume pituitary center, we have created a series of tables outlining our experience over the past 8 years (Tables 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, and 25.10). Since April 2008, our center has treated 107 patients with acromegaly (Table 25.4), 100 (93.5%) of whom were treated with the operating endoscope (Table 25.5). The majority of these patients present with tumors that stain positive for GH only (66.0%), followed by GH/PRL positive tumors (14.0%), and mammosomatotroph tumors (11.0%) (Table 25.6). Silent GH, silent MST, and silent GH/PRL tumors are less common, as are plurihormonal tumors and acidophil stem cell tumors. Of the 100 patients treated endoscopically, 16 (16.0%) had undergone prior transsphenoidal surgery for acromegaly (Table 25.8), 3 (3%) were referred for postoperative radiation therapy (Table 25.9), and 14 (14.0%) were

Table 25.4 Microscopic and endoscopic transsphenoidal surgery for acromegaly, 2008–2015

	Total (n = 107)
Demographics	
Male (no., %)	51 (47.2)
Age (yrs., range)	47.0 (16–77)
Length of follow-up (mos. ± SD)	5.14 ± 6.33
Use of endoscope[a] (no., %)	100 (93.5)
Prior pituitary surgery (no., %)	18 (16.8)
Postoperative management (no., %)	
Radiation therapy	3 (2.7)
Medical therapy	16 (15.0)

[a]See Table 25.2

Table 25.5 Endoscopic transsphenoidal surgery for acromegaly, 2008–2015

	Total (n = 100)
Demographics	
Male (no., %)	44 (44.0)
Age (yrs., range)	47.3 (16–77)
Length of follow-up (mos. ± SD)	5.31 ± 6.49
Prior to pituitary surgery (no., %)	16 (16.0)
Preoperative treatment (no., %)	
Cabergoline	5 (5.0)
Somatostatin analog	14 (14.0)
Lipid-lowering agent	15 (15.0)
Antihypertensives	26 (26.0)
Oral diabetes medications	8 (8.0)
Postoperative management (no., %)	
Radiation therapy	3 (3.0)
Medical therapy	14 (14.0)

prescribed medical therapy in the form of cabergoline (7.1%), somatostatin analogs (92.9%), and/or a GH receptor antagonist (14.3%) (Table 25.10). With the help of these adjuvants postoperatively and the careful surgical techniques detailed above, acromegaly can often be controlled, with normal or "safe" [2] levels of GH and a low complication rate (Table 25.7).

Postoperative Management and Outcomes

Postoperatively, the patients usually emerge from anesthesia in the recovery room and are sent to the neurosurgical ward, where the nurses are well versed in caring for patients with pituitary disorders. Careful attention is paid to fluid intake and

Table 25.6 Pathologic analysis for patients undergoing endoscopic transsphenoidal surgery for acromegaly, 2008–2015

	Total (n = 100)
Immunohistochemical staining (no., %)	
GH only	66 (66.0)
GH/PRL	14 (14.0)
MST	11 (11.0)
Silent MST	2 (2.0)
Silent GH	2 (2.0)
Silent GH/PRL	1 (1.0)
GH/PRL/ACTH	1 (1.0)
GH/PRL/FSH/TSH	1 (1.0)
GH/ACTH	1 (1.0)
GH/PRL/ACTH/FSH/LH	1 (1.0)
Atypical	10 (100)
Acidophil Stem Cell	1 (1.0)

Table 25.7 Complications in patients undergoing endoscopic transsphenoidal surgery for acromegaly, 2008–2015

	Total (n = 100)
SIADH	11 (11.0)
Transient DI	3 (3.0)
Permanent DI	0
Delayed CSF leak	0
Epistaxis	2 (2.0)
Meningitis	1 (1.0)
Sinusitis	2 (2.0)
Abdominal incision dehiscence	1 (1.0)
Readmission within 30 days	12 (12.0)

output, and serum sodium is measured and tracked every 6 h for the first 2 days to detect any signs of diabetes insipidus or SIADH. Morning fasting serum cortisol is measured the first 2 days after surgery in those patients who are not on corticosteroid therapy. Early ambulation is encouraged and a prophylactic anticoagulation routine is used only when there is a high index of suspicion for deep venous thrombosis. The preoperative routines for hypertension control and diabetes mellitus management are adjusted if necessary as a result of changes that can occur in the postoperative period. Many successfully treated patients find that their fingers and joints are more flexible, that the preoperative excess perspiration is gone, and that the facial features appear more youthful within the first few postoperative days. Some will experience a postoperative diuresis and associated weight loss, which we believe is the release of retained interstitial fluid by the soft tissues that have hypertrophied as a result of acromegaly.

Most of our patients return to clinic a week after surgery to determine serum sodium, and to adjust cortisol management if necessary. Because IGF-I falls slowly

Table 25.8 Patients undergoing repeat endoscopic transsphenoidal surgery for acromegaly, 2008–2015

	Total (n = 16)
Demographics	
Male (no., %)	5 (31.3)
Age (yrs.)	44.0
Preoperative treatment (no., %)	
Cabergoline	3 (18.8)
Somatostatin analog	5 (31.3)
Lipid-lowering agent	1 (6.3)
Antihypertensive	3 (18.8)
Oral diabetes medication	2 (12.5)
Complications (no., %)	
SIADH	0
Transient DI	1 (6.3)
Permanent DI	0
CSF leak	0
Epistaxis	0
Delayed meningitis	0
Readmission within 30 days	0
Pathology (no., %)	
Immunohistochemical staining	
GH only	11 (68.8)
GH/PRL	2 (12.5)
MST	2 (12.5)
Atypical	2 (12.5)
Invasive	0
Acidophil stem cell	0

and may take 2 or 3 months to normalize after successful surgery [14], we usually defer assessment of this hormone until the 3-month postoperative check-up when the definitive postoperative MRI scan is done [14]. If earlier confirmation of the success of surgery is required, 2–3 weeks after surgery an oral glucose tolerance test with growth hormone measurements can provide fairly accurate information as to whether the growth hormone axis has normalized [2].

Success rates in achieving postoperative remission of acromegaly depend upon the size and stage of the tumor, and to some degree the extent of the elevation of IGF-I and basal growth hormone. Current success rates with growth hormone–secreting microadenomas approach 80%, and for macroadenomas they are in the range of 50–60% [2, 3, 16, 23, 30]. Patients who do not achieve remission of symptoms and normal laboratory values may benefit from medical therapy, and occasionally from postoperative radiation therapy or radiosurgery [31]. Among our last 100 patients with acromegaly only three have been referred for radiation therapy. This is attributed to the success of combined management with surgery and medical treatment, which continues to be increasingly effective.

Table 25.9 Patients referred for postoperative radiation after endoscopic transsphenoidal surgery for acromegaly

	Total (n = 3)
Demographics	
Male (no., %)	1 (33.3)
Age (yrs.)	62.0
Preoperative treatment (no., %)	
Cabergoline	0
Somatostatin analog	1 (33.3)
Lipid-lowering agent	1 (33.3)
Antihypertensive	3 (100)
Oral diabetes medication	0
Complications (no., %)	
SIADH	0
Transient DI	0
Permanent DI	0
CSF leak	0
Epistaxis	0
Meningitis	0
Readmission within 30 days	0
Pathology (no., %)	
Immunohistochemical staining	
GH only	2 (66.7)
GH/PRL	1 (33.3)
Atypical	1 (33.3)
Invasive	1 (33.3)
Acidophil stem cell	1 (33.3)

Complication Avoidance in Endoscopic Pituitary Surgery

1. *Make the diagnosis*– Typical clinical features, laboratory evaluation (full pituitary hormone evaluation, Ca++, lipids, diabetes mellitus workup), cardiovascular evaluation, musculoskeletal and dental evaluation, respiratory and sleep apnea evaluation, imaging studies (MRI, bones and joints as indicated, CTA if vascular disease is anticipated). Visual evaluation including visual acuity, visual fields, fundoscopy, and OCT if indicated. One should also consider the possibility of the very uncommon hereditary causes of acromegaly, namely, the MEN-1 syndrome and Carney complex.
2. *Assess for and address comorbidities*– Diagnose and treat cardiovascular disease, cerebrovascular disease, diabetes mellitus, sleep apnea, arthropathies, sinonasal and airway pathology, elevated prolactin, carpal tunnel syndrome, colon polyps, and other neoplastic disease.
3. *Consider pretreatment with somatostatin analogs to alleviate comorbiditiesand reduce size of tumors*– Although seldom utilized in the United States, there is some argument to be made for improving the general medical condition of the

Table 25.10 Demographics of patients requiring postoperative medical therapy after endoscopic, transsphenoidal surgery for acromegaly

	Total (n = 14)
Demographics	
Male (no., %)	8 (57.1)
Age (yrs. ± SD)	44.0 ± 15.0
Prior pituitary surgery (no., %)	5 (35.7)
Postoperative prescription (no., %)	
Somatostatin analog	13 (92.9)
GH receptor antagonist	2 (14.3)
Cabergoline	1 (7.1)
Preoperative treatment (no., %)	
Cabergoline	1 (7.1)
Somatostatin analog	10 (71.4)
Lipid-lowering agent	1 (7.1)
Antihypertensive	1 (7.1)
Oral diabetes medication	0
Complications (no., %)	
SIADH	3 (21.4)
Transient DI	1 (7.1)
Permanent DI	0
CSF leak	0
Epistaxis	0
Meningitis	0
Readmission within 30 days	3 (21.4)
Pathology (no., %)	
Immunohistochemical staining	
GH-staining	14 (100)
PRL-staining	8 (57.1)
ACTH-staining	6 (42.9)
TSH-staining	3 (21.4)
LH-staining	4 (28.6)
FSH-staining	3 (21.4)
Atypical	2 (14.3)
Invasive	3 (21.4)
Acidophil	1 (7.1)

patient prior to considering surgery. A treatment trial of 3 months or so with a somatostatin analog may reduce the impact of some of the comorbidities and make the patient a better candidate for surgery and anesthesia. There is some debate about whether the potential shrinkage of the tumor and response to somatostatin analogs can improve the results of surgery, by making a large tumor more accessible to surgical resection [2].

4. *Consider obtaining an anesthesia consult prior to surgery*– It is helpful to the anesthesiologist to have advance warning of the patient with acromegaly, and to

be able to anticipate dealing with some of the unique problems associated with this condition. In addition to the general cardiac and respiratory assessment and management, many patients with acromegaly have hypertrophy of the upper airway structures and tongue, and represent challenges with regard to endotracheal intubation. In many cases using awake fiberoptic intubation is a prudent precautionary procedure.

5. *Surgical aspects*– The positioning of the patient on the operation table: The head is positioned so that it is parallel to the walls of the operating room and the midline of ambient space is identical to the midline of the patient. In order for the surgeon to operate comfortably, the head is tilted with the left ear to the left shoulder and the table angulated and tilted slightly to the right (Fig. 25.3). In most cases the thorax is elevated 25–30° to improve venous drainage and respiratory function [22]. The abdomen is prepped and draped so that a subumbilical incision can be made to obtain a fat graft if necessary. In extended cases, we prepare the distal thigh so that a fascia lata graft can be obtained for closure of the skull base defect. When image guidance is used, the head is fixated in a suitable headrest to maintain accuracy.
6. *The approach* – In acromegaly, the distances from the nasal aperture to the base of the skull are longer [28]. In addition, the mucous membranes of the nasal passage are often engorged and thickened, and may be associated with nasal polyps. Evaluation should be made for the presence of septal deviations or lateral septal spurs that may need to be resected. The bony structures of the nose and sphenoid are enlarged and quite vascular, so stout instruments and careful hemostasis using bone wax may be necessary.
7. *Surgical anatomy*– During the exposure of the bony septum and the elevation of posterior septal mucosal flaps, the sphenopalatine arteries and their branches are encountered on either side of the keel of the vomer, and must be carefully handled and preserved, with careful hemostasis necessary to avoid postoperative epistaxis. The preoperative imaging assessment will display the size and position of the internal carotid arteries. In acromegaly they may be affected by atherosclerosis, they may be enlarged or unusually tortuous, and at times they may actually be nearly touching each other in the coronal plane (Fig. 25.1). Concern regarding the carotids and their vulnerability can be further evaluated preoperatively using CT angiography. Preoperative imaging should also display the extent and position of remaining normal pituitary gland. This is an important information for the surgeon and for the surgical technique if the gland and its function are to be spared. Septation within the sphenoid sinus is another critical factor. Lateral septations often lead directly to the cavernous carotid artery. Central septations are often a useful guide to the floor of the sella. The floor of the sella may also be thicker than usual, and in some cases may be invaded by the tumor. Wide removal of the sellar floor is generally advisable, with exposure of the dura from one cavernous sinus to the other, and from the tuberculum to the junction of the sella with the clivus [4, 18].
8. *The sellar phase*– The exposed dura is evaluated for tumor invasion. The dura is interrogated with the ultrasonic micro Doppler to determine the position of the

carotid arteries and to avoid any injury to them. A dural incision is then made, either in a cruciate or an x-type fashion. Dura that is grossly involved with tumor is resected and sent to pathology. A careful subdural dissection attempting to develop a plane around the pseudocapsule of the tumor is then begun using a right angle blunt hook or the Hardy dissectors. In acromegaly, the tumors are usually white and soft and clearly different from the surrounding normal gland. A radical removal is attempted, as even a small amount of residual tumor can result in failure to achieve a remission. This occasionally necessitates the removal of tumor from the cavernous sinus, which is best done with blunt curettes and careful suction. The venous bleeding that can occur when tumor is removed from the cavernous sinus can usually be controlled by tamponade with gelfoam, and may be assisted by elevating the head of the operating table. If radical removal of the tumor results in a spinal fluid leak, the carefully sized abdominal fat graft is placed within the sella, and is held in place with the sellar reconstruction using bone, cartilage, or an artificial plate (MedPor), covered with a pledget of gelfoam to avoid exposure to the air within the sphenoid sinus. Hemostasis along the margins of the posterior septectomy and the mucosal flaps is also important, and usually allows closure without the use of nasal packing. At the end of the procedure, the nose is set to midline position and the middle turbinates are gently medialized. Fat and facial graft sites are closed with subcuticular technique.

9. *Postoperative management*– The intensive care unit can usually be bypassed in uncomplicated patients, provided that the nursing staff on the neurosurgical floor has received in-service instruction, and understands the complexities of patients who may develop disorders of fluid balance or hormonal insufficiency [22]. Careful monitoring of intake and output is essential, and serum sodium is checked every 6 h for the first 2 days. Patients who are not receiving corticosteroid replacement have fasting morning cortisol levels checked every day they are in hospital. Routine nasal care with saline sprays and occasional use of decongestants begins on the second postoperative day. We are careful about limiting fluid intake after the patient is dismissed, and postoperatively reevaluate the corticosteroid status and sodium homeostasis at a one-week visit. Patients are cautioned to report immediately if they develop severe headache, fever, stiff neck, nausea/vomiting, or fluid drainage from the nose [32]. Those who have had intraoperative spinal fluid leaks are cautioned to avoid lifting or bending with a two-pound weight lifting limit. They are also encouraged to use a stool softener.

Conclusions

These measures have stood the test of time and a clinical experience with more than 5900 transsphenoidal operations over the past 48 years, the last 600 of which have been done using the operating endoscope. Exciting advances, both conceptual and technical, continue to develop, and they expand the utility, safety, and versatility of this segment of neurosurgical practice. Most importantly, they respect the basic principles of skull base surgery (Table 25.11) which have been our guide in improving outcomes and avoiding complications.

Table 25.11 Essential principles of skull base surgery

Understand and respect the anatomy
Remove obstructing bone
Obtain wide and thorough exposure
Minimize brain retraction
Preserve and protect vital structures – arterial, venous, cranial nerves
Use microsurgical technique with two-handed microdissection
Reconstruct the anatomy and physiology

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Transsphenoidal Surgery for Prolactinomas

26

Won Kim, Srinivas Chivukula, Anthony Heaney, Marilene Wang, and Marvin Bergsneider

Introduction

Prolactinomas are the most common form of pituitary tumors, comprising 30–40% of all pituitary adenomas, with a reported prevalence of 100–775 per million people [1–3]. The presentation of symptoms in prolactinomas is unique in that patients manifest differently based on gender, age, and the size of the tumor. Currently, the general consensus is that the primary treatment modality is dopamine agonist medical therapy. Cabergoline is highly effective in normalizing prolactin levels and reducing tumor size, resulting in cure in a small percentage of patients and effective control in the majority, with a reasonably low rate of side effects and pharmacologic resistance. Surgical treatment is second-line therapy and is offered when medical management fails or cannot be tolerated. Patient selection is paramount for success, with large tumor size and cavernous sinus invasion being negative prognosticators.

Electronic supplementary material: Supplementary material is available in the online version of this chapter at 10.1007/978-3-319-56691-7_26. Videos can also be accessed at http://www.springerimages.com/videos/978-3-319-56689-4.

W. Kim, MD (✉) • S. Chivukula, MD • M. Bergsneider, MD
Department of Neurosurgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
e-mail: wonkim@mednet.ucla.edu

A. Heaney, MD PhD
Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

M. Wang, MD
Department of Head and Neck Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_26

Surgical expertise also plays an important role in success. In clinical practice, the decision-making process is sometimes nuanced, and in highly select cases, consideration may reasonably be given for primary surgical extirpation.

Interpreting Failure and Limitations of Medical Management

Per the 2006 Pituitary Society guidelines, medical management with a dopamine agonist should be considered the first-line treatment for prolactinomas, whereas surgery should be reserved for very specific patients who have (1) intolerance to dopamine agonist medications, (2) tumors that fail to respond to medical therapy, or (3) neurologic symptoms (e.g., vision loss, cranial nerve defects) due to failed medical therapy or pituitary apoplexy [4, 5]. For the surgeon, it is important to have an understanding of what constitutes intolerance and/or medical failure because criteria and definitions vary; plus, for a significant proportion of patients there are nuances and variations that impact surgical decision making.

The therapeutic goals for the medical treatment of prolactinomas are (1) normalization of prolactin levels, (2) reversal of the endocrinologic sequelae of hyperprolactinemia, (3) reduction and/or elimination of any mass effect caused by larger lesions, and if possible (4) cure. It is important to note that the latter, cure, can be achieved in only a minority of patients with this approach and is therefore not the primary goal. For any individual patient, some of these goals may be of lesser importance, depending upon age, gender, and other factors. There may be limitations forced by side effects and/or adverse events of medical treatment or, in other cases, unresponsiveness to treatment.

Dopamine agonist therapy is highly effective in normalizing prolactin levels in prolactinoma patients. Cabergoline has proven to be more effective and has lower side effects than bromocriptine [6]. In an early randomized controlled trial, cabergoline successfully reversed hyperprolactinemia in 80% of patients within 24 weeks of onset [7]. Meta-analysis of subsequent published studies suggests even higher rates, with normalization being achieved in 92–93% for cabergoline (76% for bromocriptine) [8]. The improvement is likely accounted for by study design, as responsiveness is typically limited by side effects. By treating through side effects, Ono et al. [9] demonstrated that prolactin levels could be normalized in nearly every patient with very high dosing. Failure to normalize prolactin levels should not be an absolute indication for surgery, as mild hyperprolactinemia may be asymptomatic in males and/or of minimal consequence to some female patients. Moreover, normalization of prolactin can occur with minimal change in tumor size [10].

Cabergoline decreases tumor size, to some degree, in up to 93% of patients [11]. Complete tumor disappearance on imaging is seen in almost one third of patients [12]. With cabergoline, 10–15% fail to achieve 50% reduction in tumor size [13, 14]. Discordant changes can occur, with dramatic tumor response without normalization of prolactin levels [10]. In practice, continued tumor mass effect can be problematic, with large macroadenomas continuing to impinge upon the optic chiasm (nearly exclusively males), or pregnancy-related estrogen surge-induced mitotic activity of

lactotroph cells can cause problematic tumor enlargement of macroprolactinomas, with a 22–39% risk of clinically significant tumor growth during pregnancy [15, 16].

In some situations, the lack of tumor reduction with dopamine agonist therapy is not due to tumor resistance, but rather nonresponsiveness of a clinically nonfunctional pituitary adenoma causing stalk effect-induced hyperprolactinemia [17]. Inexperienced practitioners may misinterpret the normalization of prolactin levels in this scenario as an indication of dopamine agonist responsiveness, not understanding that the effect is nonspecific (i.e., acting on normal lactotrophs). In our experience, stalk effect-related hyperprolactinemia is uncommon in adenomas less than 15 mm in size unless the tumor is nearly entirely suprasellar [18], and therefore smaller tumors with modestly elevated prolactin are often prolactinomas (assuming pharmacologic and medical etiologies of hyperprolactinemia are excluded). Conversely, prolactinomas >15 mm in size nearly always have prolactin levels much greater than 200 ng/dL, and therefore stalk effect is typically easy to recognize.

Given the reported high response rate exceeding 90% with medical management, one would expect that surgery for prolactinomas would be relatively rare (< 4% of cases assuming 35% of pituitary tumors are prolactinomas). Among our most recent 490 endoscopic endonasal surgeries for pituitary tumors (2008–2015), 79 (16%) were for prolactinomas, indicating that medical management has other limitations. A recent meta-analysis demonstrated that only 35% of prolactinoma patients continue with normoprolactinemia following the withdrawal of cabergoline therapy. Exclusion of the study by Colao et al. [19], a statistical outlier, from the analysis decreased this "cure" success rates for microadenomas to 19% and macroadenomas to 12% [20]. This highlights the fact that for the great majority of patients, lifelong medical management must be considered, which in turn raises its own set of clinical considerations. Patients with mild-to-moderate side effects are often able to tolerate a limited (2-year) medical management trial, but when confronted with the prospect of lifelong treatment, they may welcome a consideration for surgical treatment. Even among patients who tolerate dopamine agonist therapy with few or no side effects, lifelong treatment may have negative quality-of-life ramifications, including expense, hassle, and fear of interrupted medical insurance coverage.

Issues related to infertility and pregnancy are often of high importance to women with prolactinomas who are of childbearing age. Hyperprolactinemia can cause infertility in women, even in patients with normal menses presumably due to luteal deficiency [21]. Even if conception is possible with dopamine agonist therapy, some women may remain concerned about possible effects to the fetus despite studies suggesting that both bromocriptine and cabergoline are safe in fetal development [22]. Additionally, for a woman who is concerned about the number of potential childbearing years left available to her, waiting multiple years to determine if dopamine agonist treatment is effective may not be a viable option. If the tumor is surgically favorable, medical management may be the secondary modality for these patients.

Higher doses of dopamine agonists increase the likelihood or severity of side effects. Although dopamine agonist intolerance is reported to be approximately 3% with cabergoline (bromocriptine 12%) [7, 13, 14], the incidence of side effects is much higher. Common side effects include nausea (31%), headache (30%),

dizziness/vertigo (25%), and abdominal pain (15%) [7]. New-onset behavior changes occur in only 3%, but of concern is the treatment of patients with preexisting psychiatric diseases, particularly schizophrenia, bipolar disorder, and severe depression. In our practice, great caution is used in treating psychiatric patients with dopamine agonists due to the risk of exacerbation of their psychiatric illness [23, 24]. The risk of cardiac valvular insufficiency with prolonged, very high dosing of cabergoline is a low and rarely encountered clinical scenario [25, 26].

In addition to intolerance to side effects, 12% of prolactinomas will be refractory to dopamine agonist treatment, defined as the inability to normalize prolactin and less than 50% reduction in tumor size [27]. Familial syndromes, particularly multiple endocrine neoplasia type 1, account for 9% of resistant prolactinomas [6]. The failure to respond to typical cabergoline dosing conveys a level of resistance, which may portend a more aggressive biological behavior [28]. In a multicenter study of 92 patients with medically resistant prolactinomas, four patients (4.3%) developed aggressive tumors and three (3.3%) pituitary carcinoma [29]. A more aggressive treatment strategy, including surgery when appropriate, should be considered in the face of medical resistance.

Other indications for surgery include patients with large prolactinomas who present with sudden severe visual loss due to apoplexy. These are nearly always male patients, as it is rare to discover a woman with a large prolactinoma unless they have had an oophorohysterectomy or were misdiagnosed with premature menopause. Dopamine agonist treatment induces apoplexy in 2–7% of treated macroadenomas [30]. Medical treatment of giant tumors that have eroded the anterior skull base can rarely cause cerebrospinal fluid (CSF) rhinorrhea that must be treated surgically [31–33].

Prognostic Factors for Surgical Treatment

In principle, surgery shares the same therapeutic goals listed above for medical management. In practice, however, the primary goal is definitive cure rather than disease control per se. As such, the treating team must carefully analyze each tumor to assess the prospect of cure, considering factors such as (1) tumor size, (2) evidence of tumor invasion, and (3) surgical experience. Published surgical series may provide ballpark estimates of expected surgical outcomes, but these must be interpreted in context as they are generally retrospective in nature and employ variable and/or inadequate outcome criteria and follow-up. Furthermore, relatively recent advances in technology and surgical technique now allow better preoperative assessment of invasion as well as improved ability to completely remove tumors.

Numerous studies corroborate early findings that microprolactinomas have significantly higher rates of surgical cure when compared to their macroadenoma counterparts (Table 26.1). As an extension to this observation, it has been reported in many series that chances of normoprolactinemia following transsphenoidal surgery are significantly improved with purely intrasellar macroprolactinomas versus their counterparts with suprasellar or cavernous sinus extension [16, 31, 33–35]. Even within the microadenoma subset, those that were purely sellar had improved long-term rates of remission [31, 32, 34]. A recent review of 53 surgical series by Gillam and colleagues revealed that the initial biochemical cure rate following

Table 26.1 Prolactinoma surgery – demographics and outcomes

Study	Year of publication	No. of patients	Pituitary center?	Females (%)	Adenomas		Initial remission		Long-term remission (%)		Surgical cure rate (%)		Recurrence rate (%)	Follow-up duration (months)
					micro (%)	Macro (%)	rate (%)	Time from surgery	rate (%)	Time from surgery[a]	microadenoma	Macroadenoma		
Smith et al.	2015	66	Yes	44 (66.7)	39 (59.1)	27 (40.9)	42 (72.4)	NR	28 (48.3)	6 months	NR	NR	0	12
Vale et al.	2013	13	Yes	8 (61.5)	1 (7.7)	12 (92.3)	10 (76.9)	<56 days (8 weeks)	NR	Follow-up, mean 48 months	1 (100)	9 (75)	0	48
Ikeda et al.	2013	138	Yes	138 (100)	21 (15.2)	117 (84.8)	105 (76.1)	7–10 days	NR	12 months	18 (85.7)	87 (74.4)	5 (3.6)	144
Tamasauskas et al.	2012	32	No	32 (100)	32 (100)	0	19 (59.4)	<7 days	NR	48 months	19 (59.4)	NA	NA	50.4
Primeau et al.	2012	63	Yes	45 (71.4)	27 (42.9)	36 (57.1)	29 (46)	<7 days	NR	12 months	17 (63.0)	12 (33.3)	15 (23.5)	36
Berkmann et al.	2012	29	No	17 (58.6)	11 (37.9)	18 (62.1)	11 (37.9)	NR	11 (37.9)	12 months	6 (54.5)	5 (27.7)	2 (6.9)	43.2
Babey et al.	2011	34	Yes	30 (88.2)	24 (70.6)	10 (29.4)	32 (94)	<5 days	NR	3 months	22 (91.7)	10 (100)	3 (8.9)	33.5
Qu et al.	2011	87	No	0	18 (20.7)	69 (79.3)	46 (52.9)	<7 days	35 (40.2)	36 months	15 (83.3)	31 (44.9)	9 (19.6)	48
Sinha et al.	2011	172	No	71 (41.3)	16 (9.3)	156 (90.7)	62 (50.8)	<7 days	54 (44.3)	12 months	11 (91.7)	51 (46.4)	14 (8.1)	38.6
Raverot et al.	2010	94	No	62 (66.0)	43 (45.7)	51 (54.3)	60 (63.8)	<14 days	53 (56.4)	12 months	40 (42.6)	20 (21.3)	11 (11.7)	138
Sughrue et al.	2009	253	Yes	220 (87.0)	99 (39.1)	154 (60.9)	123 (59.7)	<14 days	123 (59.7)	36 months	NR	NR	8 (3.9)	42
Kars et al.	2009	23	No	15 (65.2)	0	23 (100)	8 (34.8)	7–10 days	8 (34.8)	6 months	NA	15 (65.2)	3 (13)	122.4
Kreutzer et al.	2008	212	Yes	133 (62.7)	56 (26.4)	146 (68.9)	91 (53.2)	<7 days	73 (42.7)	24 months	47 (83.9)	44 (38.3)	17 (8)	19.6
Hamilton et al.	2005	18	Yes	16 (88.9)	9 (50)	9 (50)	12 (66.7)	7–10 days	12 (66.7)	Follow-up, mean 50 months	8 (88.9)	4 (44.4)	2 (11.1)	50

A review of the published clinical series from the last decade on patients who underwent surgery for prolactinoma is summarized. Patient characteristics including age, gender, and the size of the tumor were included. Clinical outcomes including initial cure rates, long-term cure rates, and rates of recurrence were reviewed as well. Articles were also assessed for whether or not the surgical treatment took place at a dedicated pituitary center or by a pituitary neurosurgeon

NR no record, *NA* not applicable

Note 1: All studies after the year 2004 which pertain to data regarding at least five patients, and in which at least one primary outcome measure under investigation was remission rate following prolactinoma surgery in adults, are included in this table. Additionally, only original investigations – retrospective or prospective – and not reviews or meta-analyses were perused and their data included

[a]Note 2: All long-term remission rates were assessed at the last follow-up available for each patient within each study reported herein; however, given that the follow-up duration for patients varied, the time point indicated in this column, for each study, was used as the earliest point at which long-term remission rates were assessed and recorded, unless indicated otherwise

transsphenoidal surgery for prolactinomas ranged from 65 to 85% in patients with microadenomas and 30% to 40% in patients with macroadenomas [36]. Rates of recurrence were similar between both groups at approximately 20%, resulting in a long-term overall cure rate of 62% and 16% in micro- and macroadenomas, respectively [15, 36]. Salvatori et al. found similar results in a review of nine of the most recent series (2008–2013) at the time of their publication that showed an initial cure rate of microprolactinomas to be 83.2%, with a recurrence rate of 10.3%, for a long-term cure rate of 74.4% [37].

There are several possible explanations for the poorer historical surgical efficacy with macroadenomas. With the greater experience with and adoption of endoscopic approaches, the success rate for macroadenomas will likely improve most [38]. Additionally, larger tumors have a higher likelihood of tumor dural invasion, which may not have been appreciated in studies prior to the availability of 3-Tesla MRI imaging. Even with high-resolution imaging, cavernous sinus invasion is uncertain in many cases and, if present, portends a greatly lower likelihood of remission [39]. In our experience, frank cavernous sinus invasion [40] carries an extremely low chance of long-term remission for prolactinomas.

A questionable prognostic factor in surgical outcomes of prolactinoma surgery is the preoperative usage of bromocriptine causing tumor fibrosis [41–45], a finding refuted by multiple other studies [16, 32, 46–49]. A similar effect has not been reported with cabergoline [50].

The role of surgical experience is also contentious in nature. It is increasingly accepted that patient outcomes are better when treated in high-volume specialty centers, with a similar argument advanced in pituitary surgery. An overview of the clinical series published within the past decade reveals that even with the abovementioned patient selection for the most surgically curable lesions, patients who undergo treatment at a center without a dedicated pituitary surgeon have the lowest rates of surgical cure (Table 26.1). Indeed, the rates of initial cure in microprolactinomas that undergo surgery outside dedicated pituitary centers ranged from 42.6% to 83.3%, compared with 63% to 100% cure rates in patients that received surgery at dedicated pituitary centers (without the 63% outlier, range 83.9%–100%) (Table 26.1). This brings to light the difficulty of comparing surgical outcomes, with a number of enfolded variables, including surgeon experience and the use of the endoscope versus microscope, to relatively consistent and standardized medical therapy.

As surgical techniques and technologies continue to improve in the hands of dedicated pituitary surgeons, it is likely that the rates of long-term postoperative cure in prolactinoma patients will continue to improve. Given the functional nature of these tumors, even microscopic remnants of tumor cells can lead to delayed recurrence of hyperprolactinemia.

A high surgical volume alone does not necessarily guarantee excellent results since surgical technique may factor in as well. The pseudocapsular resection of pituitary tumors is a technically challenging technique that will significantly improve the efficacy of surgical management of prolactinomas. This technique was advanced by Oldfield and Vortmeyer for Cushing's disease, where they demonstrated extraordinarily high long-term remission rates for that analogous disorder [51]. Utilizing the pseudocapsular resection technique for prolactinomas, Ikeda and

colleagues achieved cure rates of 85.7% and 74.4% in micro- and macroadenomas, respectively, with only a 3.6% rate of recurrence following a remarkable 12-year mean follow-up [16]. They credited their surgical outcomes to the notion that the tumor pseudocapsule, which is normally left behind with standard pituitary surgery, harbors tumor cells in many cases. Video 26.1 shows an example of pseudocapsular resection of a 13-mm prolactinoma.

As with all conditions, proper patient selection will achieve the best surgical results. At our center, prolactinoma patients who fail an adequate trial of cabergoline are considered optimal candidates for surgery if (1) close scrutiny of the 3-Tesla pituitary MRI reveals no evidence of cavernous sinus invasion, (2) there is no prior pituitary surgery, and/or (3) there is a recent apoplexy event. Cases with cavernous sinus invasion on MRI either continue medical therapy and/or are referred for radiation therapy. For the calendar years 2014–2015, 17 of 24 cases met these criteria. A complete pseudocapsular resection was technically possible in 12/17 (71%), achieving remission in 100% of these cases (total remission rate 15/17, or 83%). The seven noncriteria surgical cases included apoplexy (two), prior transsphenoidal surgery (two), ectopic clival tumor (one), purely suprasellar tumor (one), and an intrainfundibular tumor (one), with a remission rate of only 43% in this challenging group.

Patients with medically resistant tumors may benefit from surgery, even if noncurative. In a study of 14 patients, debulking surgery had a higher rate of prolactin control ($P = 0.006$) and a significant reduction in cabergoline dosing ($P = 0.001$) postoperatively [29].

Assessing Postoperative Remission

Numerous prognostic factors have been assessed in the surgical outcomes of patients with prolactinomas, including immediate postoperative prolactin levels and tumor characteristics. Postoperative prolactin levels have also been shown to be a prognostic indicator of long-term normoprolactinemia [52–56], with a level of <10 ng/mL being cited in many studies [52, 53, 55]. Couldwell and Weiss reported that levels <3 ng/mL were associated with no recurrence of disease [55].

Raverot et al. reported on a series of 94 patients with either macroprolactinomas or giant prolactinomas in which tumor histology and gene expression were analyzed. They identified seven genes that were upregulated in patients with either tumor recurrence or progression, and an additional five genes that were associated with the degree of invasiveness [33].

Surgical Morbidity and Mortality

Complications related to transsphenoidal surgery vary depending on the surgeon's experience and the morphology of the tumor. An analysis of the morbidity and mortality within the recent literature reveals rates of mortality of 0.2%–0.5%, CSF leak 6–7%, meningitis 1–2%, vascular injury 0.5%–1.6%, permanent diabetes insipidus 2.3%–4.3%, and hypopituitarism 8.5%–11.6% [57]. Of the reported

complications in the published series within the past decade, the rates of permanent diabetes insipidus were 0%–6.3% [13, 25, 46, 58], new anterior pituitary deficit 1.5%–7% [31, 58], and mortality 0%–1.7% [59]. Apart from one outlier in regard to patient mortality, these outcomes do not differ considerably from those in the current literature [57].

Nasal morbidity as a result of the endonasal endoscopic approach must be factored in when considering surgery [60–62]. In order to minimize sinonasal morbidity, routine partial middle turbinectomies, nasoseptal flaps, and maxillary antrostomies are not performed unless indicated. With the use of free mucosal grafts and postoperative irrigation and otolaryngology follow-up, patients experience relatively rapid recovery postoperatively, with most returning to normal sinonasal function within 1–3 months after surgery [63].

Consideration of Surgery as Primary Treatment Modality

Numerous studies have demonstrated that patients with purely intrasellar microadenomas without cavernous sinus involvement and preoperative prolactin levels <200 ng/mL undergoing transsphenoidal surgery have outcomes equivalent to or exceeding the *control* rate of medical management [32, 64], with surgical *cure* rates in many series nearing 90% [34, 52, 65, 66].

There have been conflicting arguments regarding the comparative costs of transsphenoidal surgery versus lifelong medical management. Cauldwell and Weiss [67] argued that within their own institution, the expected surgical and perioperative cost incurred for a single patient undergoing transsphenoidal prolactinoma surgery was approximately $10,000. When considering the cost of yearly dopamine agonist medication to be approximately $3300, the expected cost of medical management would outstrip that of surgery within 4 years, not to speak of serial imaging to follow the size of the adenoma in medically managed patients. They argued that in the hands of experienced pituitary surgeons with an expected near 0% mortality and minimal morbidity, transsphenoidal surgery may be a considerably more cost-effective option [67]. Bloomgarden and colleagues quoted much higher estimates of cost regarding surgery ranging from $39,000 to $74,000 based on recent literature [15]. Moreover, they argued that as the expected rate of postoperative cure within the community where most patients would likely be treated is closer to 60%, when considering a sample size of 100 patients, the savings of continued medical management versus surgery and medical management for failures of cure could be in the millions of dollars. Although conflicting conclusions, these value analyses make it clear that should transsphenoidal surgery be considered, it should be done in the hands of experienced pituitary surgeons at specialized centers in order to maximize outcomes and mitigate costs related to complications.

In regard to patient quality of life, there are reports of impaired quality of life in prolactinoma patients who have undergone either medical management or transsphenoidal surgery [68, 69]. However, a recent quality-of-life assessment in patients with functioning pituitary adenomas who undergo operative management argued that quality of life is

not impaired postoperatively in patients with prolactinomas [70]. Furthermore, it has also been shown that through the surgical debulking of prolactinomas, lower doses of medications can be used to achieve normoprolactinemia postoperatively, which may afford patients more tolerable side effect profiles [46].

Summary

Dopamine agonist therapy is the first-line treatment for the vast majority of patients with prolactinomas. However, patient selection and surgical techniques have continued to improve, keeping surgery in the hands of proficient pituitary surgeons a viable option for selected patients. It remains to be seen whether prolactinoma surgery will prove to be more cost-effective than lifelong medical management. It seems that there will be particular patient populations in which the accessibility of the lesion and high rates of cure will make a strong argument for surgical resection, namely, young patients with intrasellar adenomas without suprasellar or cavernous sinus invasion.

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Transsphenoidal Surgery for Nonfunctioning Pituitary Adenomas

27

Sarah T. Menacho and Ian E. McCutcheon

Background

Pituitary tumors account for 10% of all intracranial tumors and have an incidence of 15% [1]. Classically, pituitary tumors are divided into functional and nonfunctioning lesions. Functional lesions secrete hormones, with prolactin-secreting tumors the most common at over 50% [2]. Nonfunctioning lesions, which will be the focus of this chapter, either do not secrete hormones or secrete substances such as gonadotropins that do not typically cause functional endocrine symptoms. Nonfunctioning pituitary adenomas comprise null cell adenomas, oncocytomas, and gonadotropin-secreting adenomas; together, they account for 30% of all pituitary adenomas [3]. Nonfunctioning pituitary adenomas often come to medical attention after growing to a size sufficient to cause neurologic symptoms such as bitemporal hemianopia from compression of the optic chiasm [4]. It is important to note that while nonfunctioning pituitary adenomas do not secrete hormones, they can cause anterior hypopituitarism from compression of the normal gland [4]. Diabetes insipidus from compression of the posterior lobe is quite rare. Although nonfunctioning pituitary adenomas can also cause hydrocephalus from mass effect on the third ventricle and cranial neuropathies (III, IV, V_1, V_2, VI) from compression of the cavernous sinus, visual impairment and hypopituitarism are the most common presenting symptoms [4]. Nonfunctioning pituitary adenomas can also present with pituitary apoplexy, characterized by abrupt onset of headache, visual compromise, and endocrine derangements [5].

S.T. Menacho, MD
University of Utah, Department of Neurosurgery, Salt Lake City, UT, USA

I.E. McCutcheon, MD (✉)
University of Texas, Anderson Cancer Center, Neurosurgery, Houston, TX, USA
e-mail: imccutch@mdanderson.org

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_27

Preoperative Evaluation

Both MRI and CT scans are used to show the anatomy of a nonfunctioning pituitary tumor (Figs. 27.1a, b and 27.2). The size of a normal pituitary gland, with some minor variations, is approximately 9 mm [6]. An MRI can reveal the relationship of the tumor to the optic apparatus, the cavernous sinus, and the carotid artery, while a CT can help to delineate the bony anatomy of the sphenoid sinus and the floor of the sella. All patients undergoing surgery for nonfunctioning pituitary adenomas should

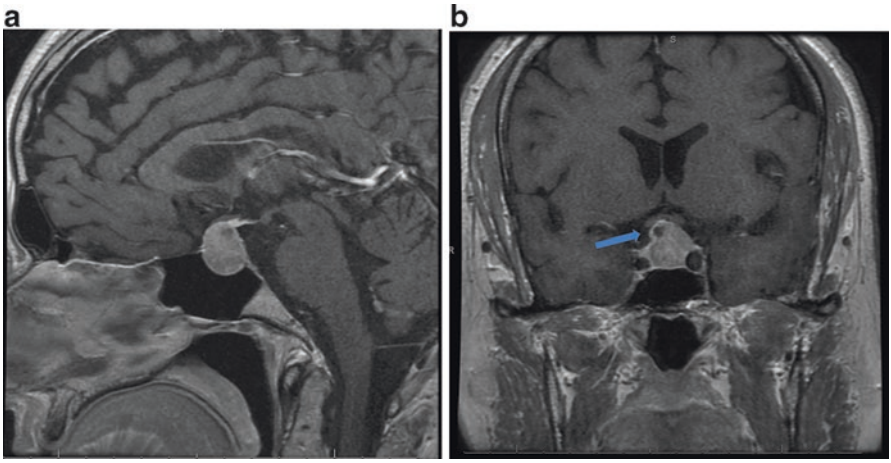

Fig. 27.1 (**a**) Sagittal T1-weighted postcontrast MRI displaying a nonfunctioning pituitary macroadenoma (**b**) Coronal T1-weighted postcontrast MRI showing a nonfunctioning pituitary macroadenoma. Note the proximity of the tumor to the optic chiasm (**blue arrow**). The chiasm is elevated slightly, and the patient retains normal visual fields but is at definite risk for loss of vision should further expansion of the tumor occur

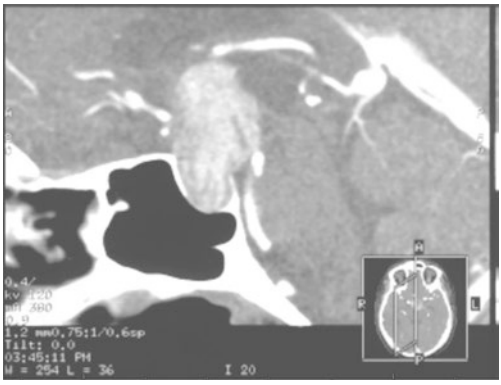

Fig. 27.2 Sagittal postcontrast CT of a patient with a pituitary macroadenoma. Note the thinning of the floor of the sella due to the mass effect of the tumor. CT shows bone with more clarity than does MRI, and can adequately display the extent of the tumor when displayed in thin cuts and multiplanar views

have a visual field examination by an ophthalmologist and an endocrine workup to reveal any loss of hormone function. Some of these patients (most typically, those with secondary hypothyroidism) will need some form of hormone replacement prior to surgical intervention.

In men the most common and earliest hormone deficit seen in the context of a nonfunctioning macroadenoma is hypogonadism. Low levels of testosterone can be profoundly disabling, compounded by the fact that a man with a macroadenoma and secondary hypogonadism is often anemic because testosterone is a growth factor enabling erythrocyte production. In patients with microadenomas and low testosterone, recovery of hormone levels after surgery usually does not occur because the degree of gland distortion is insufficient to explain the hormone deficit; thus, in such patients that deficit is not a good reason to perform tumor removal. We typically follow them over several years and operate only if the adenoma grows significantly. Even after surgery, normalization of the pituitary-gonadal axis is not guaranteed, as recovery of male reproductive hormone function has been shown to be 26% at 6 wk and 36% at 6 months, indicating that most of these patients will require long-term supplementation with testosterone [7].

As part of the preoperative evaluation, the prolactin level must be checked to determine whether the patient has a prolactinoma or a nonfunctioning pituitary adenoma. This is important because prolactinomas are often treated initially with medical management (dopamine agonists such as bromocriptine or cabergoline) as opposed to surgical intervention. As stated earlier, prolactinomas are the most common pituitary tumors, accounting for 50–60% of all functional pituitary tumors [8]. Hyperprolactinemia often presents with the triad of amenorrhea, infertility, and galactorrhea in women [8]. Conversely, prolactinomas in men are often macroadenomas (80%) [8], and usually present with signs and symptoms of mass effect (headaches, visual disturbances, and cranial nerve deficits).

A true prolactinoma typically presents with a prolactin level >250 ng/mL [8]. Stalk effect, which can be caused by a large nonfunctioning macroadenoma, produces a serum prolactin level of <100 ng/mL in over 80% of cases [8]. This is an important distinction to make in order to avoid misdiagnosing a macroadenoma as a prolactinoma, which can lead to inappropriate treatment with dopamine agonist [8]. In extremely large tumors, the sample should be diluted 1:100 to avoid the "hook effect," whereby extremely high prolactin levels may overwhelm the antibodies used in the radioimmunoassay and lead to falsely low readings [8]. Of course, other causes of hyperprolactinemia must be ruled out, including pregnancy, chronic renal failure, liver cirrhosis, hypothyroidism, and medications that inhibit dopamine reuptake (MAO inhibitors, tricyclic antidepressants, SSRIs, and antipsychotics such as risperidone and olanzapine) [8].

Nonsurgical Options

As opposed to functional pituitary adenomas (e.g., prolactinomas), the nonsurgical options for nonfunctioning pituitary tumors are quite limited. Bromocriptine has been tried in the past with slight-to-moderate reduction in tumor size in <20% of

patients [9]. For an asymptomatic pituitary microadenoma (<1 cm, discovered incidentally), serial imaging with MRI can be used to follow the tumor for interval growth if there is no evidence of visual compromise. However, nonfunctioning pituitary macroadenomas (>1 cm) or tumors that are causing neurologic/endocrine derangements must be surgically decompressed. In fact, a large nonfunctioning pituitary tumor that is elevating the optic chiasm may be surgically decompressed even in the absence of neurologic symptoms to prevent a visual field deficit from developing. Other indications for surgical resection of a nonfunctioning pituitary adenoma include the need for pathologic tissue diagnosis, pituitary apoplexy, and the development of a tumor-associated cyst compromising pituitary or visual function [10].

The incidence of clinically "silent" pituitary adenomas found at autopsy is 10–20% [6]. For incidentally discovered nonfunctioning pituitary adenomas, 10% of microadenomas and 24% of macroadenomas will display growth without intervention [6]. While these tumors are classically labeled as "nonfunctioning," 70–80% produce gonadotropins, and up to 41% of nonfunctioning macroadenomas will present with hormonal dysfunction; therefore, screening with a hormone panel is warranted [6]. Patients can be "symptomatic" and still have an incidental tumor; many present with symptoms (headaches, dizziness, or blurred vision) that are difficult to ascribe to the tumor, especially if it is small. In such patients it is wise to avoid promising symptomatic relief after treatment, and such symptoms should not be used as an indication for resecting nonfunctioning microadenomas.

If the tumor is thought to be nonfunctioning but there is suspicion of apoplexy based on radiographic findings, then the decision on surgical intervention must be based on clinical symptoms (e.g., vision loss, cardiovascular collapse). Although the incidence of apoplexy in nonfunctioning tumors is unknown, we believe that if there is evidence of prior hemorrhage on imaging but the patient is clinically stable, and particularly if he or she is without symptoms, then surveillance with repeat scan in three to four months rather than emergent surgical intervention may be a reasonable treatment strategy.

As always, any nonfunctioning tumor in the sellar region in a patient with a history of cancer, regardless of size or hormonal function, could be a metastatic lesion, with breast (6–8%) and lung the most common primary tumors to metastasize to the pituitary gland [11]. Pituitary metastases are not often symptomatic (7%) [11], but in the modern era when patients with systemic cancer are more effectively treated, those with pituitary metastases may be medically controlled in some cases, but show progression in others, leading to the hormonal deficits and loss of vision seen with nonfunctioning macroadenomas. Overall, they tend to carry a poor prognosis with survival ranging from 6–22 months [11]. When a sellar lesion is found in a patient with a cancer history and the lesion is well separated from the optic apparatus, we rescan in two to three months; many such tumors will be benign adenomas, but this strategy allows identification of the subset of true metastases that will grow more rapidly and need earlier intervention.

Figure 27.3 depicts a decision-making tree for choosing the best treatment strategy for patients who present with a nonfunctioning sellar tumor.

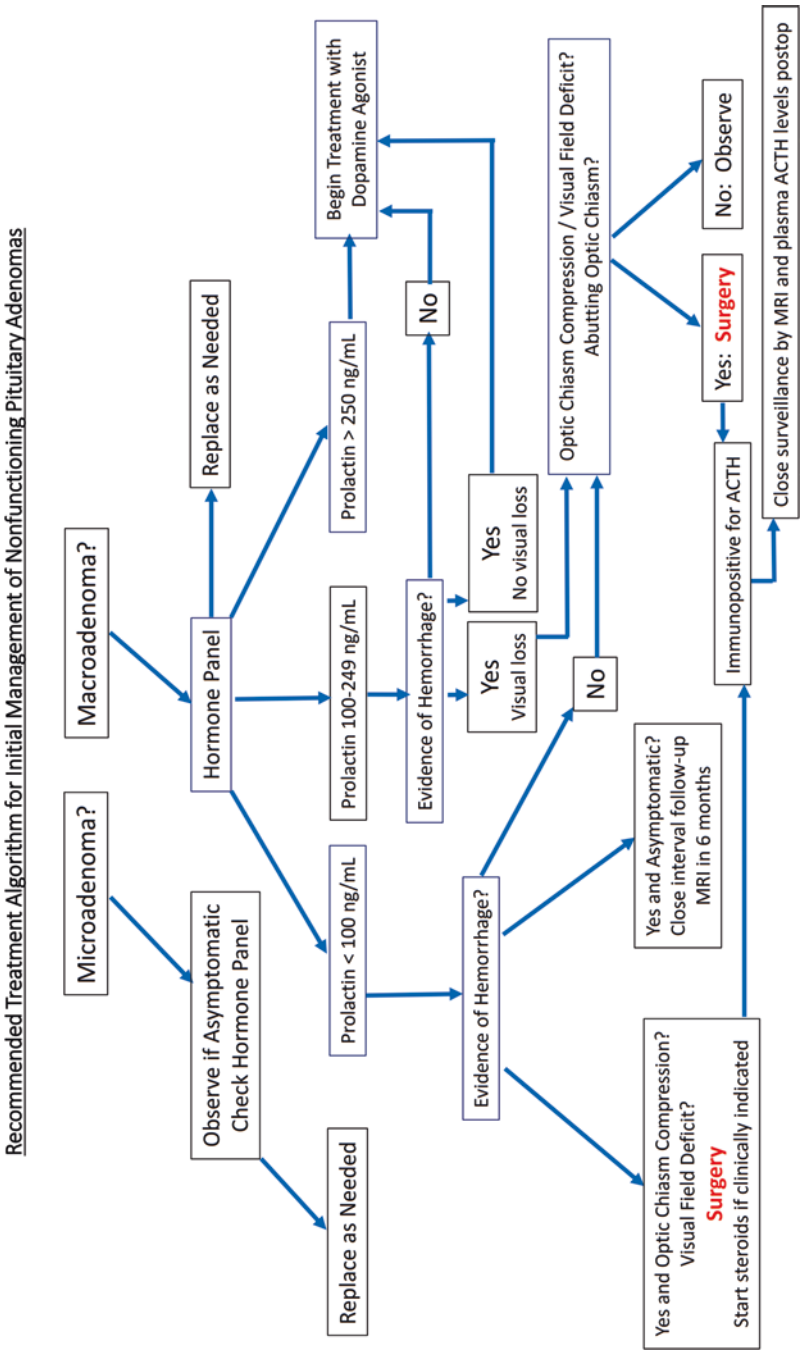

Fig. 27.3 Recommended treatment algorithm for the initial management of nonfunctioning pituitary adenomas

Surgery

In a medically fit patient, the treatment of choice for a symptomatic nonfunctioning pituitary adenoma is transsphenoidal resection by an experienced neurosurgeon [12]. The goal is to remove as much tumor as is safely possible, and to relieve endocrine, visual, and neurologic deficits. As previously stated, growth of nonfunctioning pituitary adenomas without treatment occurs in approximately 10% of microadenomas and 24% of macroadenomas [6, 13]. In patients with a significant amount of residual tumor after surgery or in those who show tumor recurrence, radiotherapy can be used [14]. Radiotherapy may not always be necessary, however, as some patients with postoperative residual tumor show little or no expansion over time, presumably due to devascularization induced by the surgical disruption of the original lesion. Studies of the natural history of such residual fragments have given variable results. Park et al. found that 15% had grown 5 years after surgery, and 50% by 10 years, while Chang et al. showed an incidence of 28% and 45% at 5 and 10 years, respectively [15, 16]. In their study the likelihood that residual fragments of tumor would grow accelerated beginning four years after surgery, and that those with cavernous sinus invasion were more likely to show growth in residual tumor [16].

Radiotherapy is not considered a primary first-line treatment for pituitary adenomas unless the patient is elderly or medically unfit for surgery, whereby it may be the only viable treatment. Furthermore, in those patients who receive irradiation after a high-volume resection of a nonfunctioning pituitary adenoma, recurrence rates have been shown to be lower than those who are followed with serial imaging: published statistics show 5- and 10-year recurrence rates of 2.3% and 2.3% vs. 15% and 50% in the group not treated with postoperative radiation [15]. These recurrence rates are variably reported in the literature, however; another study showed a recurrence rate of 10% at 8 years for nonfunctioning tumors treated with surgery followed by irradiation, with higher rates of recurrence for patients who did not get radiotherapy [16]. In fact, some residual nonfunctioning adenomas have been shown to shrink spontaneously after three months, especially smaller tumors with a cystic component and tumors that were resected in an intraoperative MRI suite [17]. This makes the role for postoperative radiotherapy somewhat controversial, as it is associated with longer periods of tumor control but also exposes the patient to increased morbidity from hypopituitarism, radiation-induced optic neuropathy, and postirradiation effect within the temporal lobe.

A transcranial approach may be considered for large suprasellar masses, those with extrasellar extension into the anterior, middle, and/or posterior fossa, tumor growing despite adequate targeting with radiotherapy, recurrent tumor with significant scarring, or a very fibrous tumor that could not be completely removed via a transsphenoidal approach done by expert hands. Even when a nonfunctioning pituitary adenoma is discovered incidentally, progression-free survival is improved (87% compared to 78%) and tumor growth is less often seen (8.9% compared to 31%) when surgery is performed as opposed to observation [17].

Invasion of the cavernous sinus has been shown in multiple studies to be a strong negative risk factor against complete surgical resection of a nonfunctioning pituitary adenoma [17, 18]. Other negative indicators against a gross total resection are

increasing tumor size and absence of apoplexy at presentation [17]. Tumor apoplexy is in fact associated with low postsurgical rates of recurrence, perhaps due to the fact that hemorrhagic and necrotic portions of the tumor may be easier to remove, or because residual tumor may be nonviable [17]. Following transsphenoidal surgery, visual function is expected to improve in over 80% of patients with impaired vision due to apoplexy when surgery is performed within 48 h of diagnosis [19]. This is compared to 73% of patients without apoplexy who experienced improvement in vision (acuity and fields) at 3 months following resection of pituitary macroadenoma [20]. In nonfunctioning pituitary adenomas as a whole, visual function is expected to improve in 80% of patients following surgery [21]. The transsphenoidal approach is much less traumatic to the optic apparatus than the transcranial approach.

Mortality following a transsphenoidal resection is generally <1%, with major complications around 5%, although the results vary based on the experience of the surgeon and the case volume of the hospital [22]. A sublabial or (most often) an endonasal approach to the sella may be used for most nonfunctioning adenomas, with visualization through a microscope or endoscope by surgeon preference. However, an extended endoscopic approach is useful for dural-based lesions with a high risk of CSF leak and for tumors with extensive suprasellar extension to which more access is needed. Such patients typically require either an extended transsphenoidal approach with nasoseptal or pericranial flap coverage of the surgical defect, or a craniotomy. In order to help avoid postoperative complications during a transsphenoidal surgery, it is important not to violate the arachnoid whenever possible, as this can lead to meningitis, CSF leak, hypothalamic injury, and injury to the optic chiasm or to surrounding vascular structures [23].

Several relevant anatomical characteristics help guide the decision on whether to do transsphenoidal or transcranial removal of a pituitary tumor. Zada et al. retrospectively reviewed a series of 250 patients who had undergone transsphenoidal resection of pituitary tumors to find those patients who were considered for (or subsequently required) open craniotomy for further tumor resection [23]. Although this series of patients included craniopharyngiomas, meningiomas, and functional pituitary tumors in addition to nonfunctioning adenomas, the relevant anatomical principles still apply. The authors identified 7 factors in 13 patient case examples that not only limited the extent of resection, but also led to increased perioperative complications: (1) significant suprasellar extension, (2) lateral extension, (3) retrosellar extension, (4) brain invasion with edema, (5) firm tumor consistency, (6) involvement or vasospasm of the arteries of the circle of Willis, and (7) encasement of optic apparatus or invasion of the optic foramina. Prior surgery or radiation therapy was also found to be a challenge for the transsphenoidal approach in this study. Some of the complications the authors encountered included subtotal resection, intratumoral hemorrhage, vasospasm, visual loss, and even death in one patient. Although there is no defined size "limit" for a transsphenoidal surgery, the mean size of the pituitary tumors for the patients in this study was 3.7 cm (range 1.5–5.5 cm), suggesting (but not proving) that perhaps tumors over 3.5 cm with one or more of the risk factors listed above may benefit from open craniotomy rather than transsphenoidal resection of their pituitary tumor. As we and others have successfully

resected and achieved long-term remission in macroadenomas extending as far as 4 cm above the sellar floor, it is difficult to establish an absolute criterion of size useful in driving the choice of surgical approach.

Postoperative Complications

Unfortunately, up to 50% of patients with nonfunctioning pituitary adenomas have some degree of hypopituitarism prior to surgical treatment [7]. Men older than 60 years with macroadenomas had a higher incidence of preoperative endocrine dysfunction in one study [7]. In another study, diabetes insipidus developed in 5.9% of patients, although this resolved in 21 of 29 patients within 2 years of surgery [24]. Most cases of DI are transient and resolve within 72 h of surgery. Postoperative hydrocephalus may develop in patients who have a tumor with suprasellar extension due to traction on the third ventricle, cerebral edema, or subarachnoid bleeding during or after tumor removal [25]. Long-term hypopituitarism is seen in 5% of cases [24]. Overall, the literature is mixed on the recovery of preoperative pituitary dysfunction, with studies showing varying incidences of improvement, worsening, and no change [26–28]. Younger age and higher preoperative gland volume (mean 0.43 cm^3) have been shown to correlate favorably with the recovery of pituitary hormonal function [7]. Persistent cerebrospinal fluid leak after surgical intervention, a known complication of transsphenoidal surgery for both functioning and nonfunctioning adenomas, was seen in only 2.6% of patients in one large study [17]. However, this small percentage may not represent the true incidence of intraoperative CSF leak which is likely higher when untreated low-flow leaks as well as high-flow leaks treated with lumbar spinal drainage are included in the definition of surgically induced CSF leak.

Recovery of vision following surgery for nonfunctioning pituitary adenomas depends on the degree and duration of the compression exerted by tumor on the optic apparatus. One large study of 103 patients with macroadenomas (78 of which were classified as nonfunctioning) showed postoperative improvement in visual field deficits in 74% of patients as evaluated by an ophthalmologist preoperatively and at 6 months postoperatively [29]. This study found that patients with pituitary macroadenomas who were operated on within six months of the onset of visual loss recovered more vision than did those in whom surgical resection was delayed longer than six months. Factors associated with poor recovery of visual deficits after resection of a pituitary adenoma include higher preoperative visual impairment scale score, larger tumor size, displacement of the optic chiasm on MRI, and optic atrophy [30].

Recurrence

Multiple studies have shown a 5-year recurrence-free survival rate of approximately 80% in patients with a gross total resection of a nonfunctioning pituitary adenoma [31, 32]. This drops to approximately 70% in patients in whom a gross total

resection could not be achieved [17]. Younger age at diagnosis is associated with a higher risk of tumor recurrence [17]. It is important to note that recurrence rates and the rate of gross total resection are similar whether the transsphenoidal surgery is done via the microscopic or the endoscopic approach [33, 34], so the choice of technique should be up to the neurosurgeon of record.

Special note should be made here of cystic pituitary adenomas, which can include both functional and nonfunctional lesions. Tumors with cystic or posthemorrhagic changes (e.g., apoplexy) may not need to be fully removed at surgery if this poses an increased risk to the patient, as these tumors have been shown to spontaneously shrink as much as 34% in size on 3-month follow-up imaging [35]. The experienced neurosurgeon should keep this in mind when weighing the risks and benefits of complete removal of a cystic pituitary lesion. In our own experience, we usually do strive to remove completely both the tumor and the wall of its associated cystic component.

Another note should be made regarding the use of intraoperative MRI when performing resection of a pituitary adenoma (functional and nonfunctional). Several studies have shown an increase in the extent of resection when the surgery is performed in either a 1.5- or 3-Tesla intraoperative MRI suite [36–38]. For nonfunctioning pituitary adenomas specifically, gross total resection rates were increased by up to 29%, even for invasive adenomas, and the detection of remnants with intraoperative MRI had a much higher sensitivity and specificity (approaching 100%) when compared with endoscopy (21% sensitivity, 78% specificity) [37]. Although the use of intraoperative MRI does increase the length of OR time (158 min versus 58 min in the non-iMRI group in one study), using this technology can lead to a higher rate of gross total resection and therefore lower recurrence rates than when only the microscope or endoscopy is used [38]. The caution we offer is that the incremental benefit of technology depends very much on the skill of the surgeon. Such tools, including both iMRI and endoscope, will logically give the greatest increase in tumor removal to the surgeon with less experience, and the least to the expert surgeon with a thousand or more cases behind him or her. Because these studies of the impact of new technology on outcome are rarely if ever normalized for surgeon experience, their conclusions should be taken as applicable to some, but not to all.

Brief mention should be given here to the category of "silent" corticotroph and somatotroph adenomas. Some clinically nonfunctioning pituitary adenomas stain for adrenocorticotropin (ACTH) or growth hormone by immunohistochemistry. The silent *corticotroph* adenomas are immunopositive for hormone production but lack the clinical manifestations of Cushing's disease because they fail to convert pro-opiomelanocortin to ACTH [39]. When compared with nonfunctioning pituitary adenomas by Ioachimescu et al., silent corticotroph adenomas demonstrated similar recurrence rates (approximately 6%), and did not appear to be more aggressive in nature [40]. However, the consensus of other authors is that this subclass of nonfunctioning adenomas recurs earlier and more often than do null cell or gonadotropin-producing adenomas due to a more invasive phenotype [39, 41]. This may reflect nosological confusion, as some silent corticotroph adenomas are actually

more appropriately classified as silent subtype 3 adenomas, some of which express ACTH, none of which produce Cushing's disease, and all of which are macroadenomas with an aggressive tendency toward growth and invasiveness [42]. The treatment for recurrent disease in this subset of patients is typically reoperation (if feasible and safe) with a low threshold for applying stereotactic radiosurgery to any unresectable residual tumor present after a first or second surgery [40]. Silent adenomas that are not causing neurologic symptoms can be followed with serial MRI scans. The clinically silent *somatotroph* adenomas represent about one-third of all adenomas expressing growth hormone, but are not known to be show a different clinical behavior than their hormonally active counterparts [43].

Radiotherapy

We generally use surgery as first-line treatment for patients with nonfunctioning adenomas deemed to need intervention. As many such tumors undergo surgery because of their proximity to the optic apparatus, this strategy avoids irradiation of a potentially compromised nerve with vulnerability to radiation-induced optic neuropathy. In addition, the selectivity of surgical removal allows better sparing of the normal pituitary gland than does irradiation of the sella. Even stereotactically focused treatment plans often must include all or some of the gland in the target area, which confers a risk of delayed hypopituitarism much higher than that seen after surgery, one that reaches 30% [44]. Finally, surgery allows a prompt and usually complete decompression of the gland and chiasm whereas tumor shrinkage after radiotherapy of whatever modality is slower and less complete.

The use of radiotherapy in our cohort of patients with nonfunctioning adenomas is limited to those meeting one or both of the following criteria. One group amenable to irradiation includes those with incompletely removed tumors that grow over time, and whose invasive features eliminate the possibility of complete removal by reoperation. These features pose the likelihood that the tumor will recur without adjuvant therapy. The second group includes those with histologically atypical or anaplastic tumors, as judged by a high preoperative rate of growth, invasion into parasellar compartments, a high MIB-1 labeling index or mitotic index, or mutant p53 immunopositivity. Each of these factors predicts early recurrence [45].

When possible, stereotactic radiosurgery (SRS) is preferable to conventional fractionated limited-field radiotherapy when the anatomy of the tumor relative to the optic nerves and chiasm is favorable. Radiotherapy controls tumor growth, but does not guarantee tumor shrinkage, in 80–98% of patients with nonfunctioning pituitary adenomas [14]. In a large 2013 multicenter analysis by Sheehan et al. combining data from nine Gamma Knife centers, 479 patients who had undergone prior resection of a nonfunctioning pituitary adenoma received SRS with 16 Gy to the tumor margin. With a median follow-up of 36 months, 93% of patients had achieved tumor control. There were no deaths during the study period, and new or worsened pituitary dysfunction was reported in 21% of the patients [46]. In fact, hypopituitarism is the most common side effect of irradiation of the pituitary gland, with an

incidence of 13–56% over the 5 years following treatment. Thus, a study with a mean follow-up interval of less than 5 years will underreport the true long-term incidence of hypopituitarism. Other important side effects included new or worsened cranial neuropathy (9%) and new or worsened optic neuropathy (6.6%). Side effects as cited by other authors include optic neuropathy in 1.7%, vascular changes in 6.3%, neuropsychological problems in 0.7%, and secondary malignancies in 0.8% [21].

A key point is that radiotherapy, including Gamma Knife radiosurgery, does not consistently reduce tumor size. Park et al. reported tumor reduction in 53% of a large cohort, most of whom were treated for residual or recurrent tumor after prior surgery [47]. No details were given on degree of shrinkage, and 10% of the patients eventually showed tumor growth. The published series on radiosurgery for nonfunctioning tumor all focus on its use as adjuvant therapy, not as primary treatment. This is appropriate because the majority of nonfunctioning tumors needing treatment are macroadenomas endangering or directly compressing the optic chiasm; thus, surgery remains the treatment of choice on initial presentation, or when decompression is desired. Despite the fact that nonfunctioning pituitary adenomas display frequent dural invasion [21], many patients with this tumor type do well for long periods of time without radiation therapy.

Follow-Up

Postoperative evaluation with MRI and CT scans should not be performed prior to 6–12 weeks after surgery because of interference from early postoperative changes. Persistent mass effect and residual blood and edema seen in the early postoperative period will slowly resolve, and this can be documented with serial MRI studies (Fig. 27.4) [48].

Patients with nonfunctioning pituitary adenomas should have annual MRI or CT scans, along with visual and endocrine evaluations whether or not they have had surgery or radiotherapy [21]. If these tumors are not treated, they continue to grow over months or years, sometimes continuously but sometimes in step-wise fashion. The recurrence rate after gross total resection has been achieved by transsphenoidal surgery is 10–20% [20]. As previously stated, a significant number of patients who undergo postoperative radiotherapy, and some who have undergone only surgery, will eventually develop hypopituitarism and therefore should be monitored on an annual basis with hormone panels.

Conclusions

Nonfunctioning pituitary adenomas account for 30% of pituitary adenomas. Surgery remains the cornerstone of treatment for these tumors. In some patients with tumor recurrence, or with gradual expansion of a residual fragment of tumor, stereotactic radiotherapy can be useful. Cystic pituitary lesions may not require gross total resection due to postoperative shrinkage of remnants. Nonfunctioning pituitary

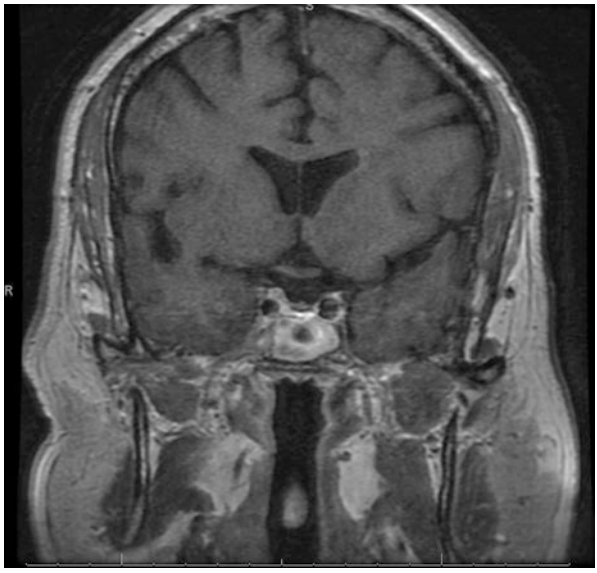

Fig. 27.4 Coronal T1-weighted postcontrast MRI done three months after surgery shows decreased mass effect on the optic chiasm and small residual disease along the superomedial aspect of the right internal carotid artery within the cavernous sinus

adenomas typically do not respond well to medical management. If the patient presents with endocrine or neurologic symptoms, or if a tumor is discovered incidentally but is large enough to endanger vision, the appropriate management is surgical intervention via a transsphenoidal approach whenever possible unless the anatomy is unfavorable. Select patients without visual compromise may be monitored with serial imaging and ophthalmological exams. Recurrence rates do not appear to be different between the microscopic and endoscopic approaches, but the use of the intraoperative MRI has been shown to increase the rate of gross total resection. The complication rate is low following these procedures, although postoperative DI is common in the perioperative setting and up to a third of initially intact patients will have some short-term pituitary dysfunction. Visual function improves in over 70% of patients and this number is even higher if the visual dysfunction is associated with pituitary apoplexy. Due to the 20% recurrence rate following resection, patients with nonfunctioning adenomas should be monitored with annual MRI or CT scans, and sooner if new symptoms develop.

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Pituitary Tumors in Pediatric Patients

28

Robert F. Dallapiazza and John A. Jane, Jr.

Introduction

Although pediatric pituitary and parasellar tumors are uncommon, they can produce significant disability and pose significant treatment challenges for pediatricians, endocrinologists, and neurosurgeons. Despite their rarity in pediatric patients, there are a wide range of lesions that affect the pituitary gland and parasellar region. Craniopharyngioma is the most common, followed by hormone-active pituitary tumors.

Fortunately, most pituitary tumors in children are benign. However, given the location of these tumors, they can have a profound impact on hormonal regulation in growing children. Therefore, surgical interventions must be planned carefully in order to minimize operative morbidity and maximize functional recovery. As with adult pituitary lesions, the transsphenoidal corridor often is a surgical option for treating pituitary and parasellar tumors in children.

In this chapter we discuss some of the surgical nuances of transsphenoidal surgery in pediatric patients. We then review the clinical presentation, operative considerations, and surgical outcomes for the most common pediatric pituitary tumors. Finally, we discuss complication avoidance and management.

Transsphenoidal Surgery in Pediatric Patients

One of the main considerations, especially for younger children, is the width of the intranasal corridor for a transsphenoidal approach. The nasal aperture, interturbinate distance, and intracarotid distance can all affect working angles to successfully achieve sellar access through the sphenoid. Banu et al. measured and reported many

R.F. Dallapiazza, MD, PhD • J.A. Jane, Jr., MD (✉)
Department of Neurosurgery, University of Virginia Health System, Charlottesville, VA, USA
e-mail: johnjanejr@virginia.edu

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_28

of the key anatomical factors for successful endonasal endoscopic transsphenoidal surgery in children. They found that many of the key restriction points increased in size gradually from childhood to adolescence, and there were significant differences in the size of these key restriction points only in the extremes of ages [1]. Tatreau et al. similarly studied limiting bony prominences in pediatric endonasal surgery and found that the size of the nasal aperture was potentially a limiting factor only among the youngest age group (less than two years old) [2].

The sphenoid sinus develops during childhood with progressive increase in aeration up to the third decade of life [3–5]. Several variations in sphenoid sinus morphology are recognized and classified based on the degree of pneumatization in relation to the sella. In adults, the most common configuration is the "sellar" in which the sellar floor and anterior sella are completely included within the sphenoid sinus. The next most common variation is the presellar configuration where the sellar floor is covered by bone followed by the conchal configuration where the sphenoid has little or no pneumatization (Fig. 28.1).

The volume of sphenoid pneumatization increases with age to until the third decade. The appearance of sphenoid pneumatization begins with growth of the sphenoid bone. The aeration process of the sinus begins as a bilateral doublet on the anterior-inferior border beginning at one to two years of age and the volume of the sphenoid sinus increases until the second or third decade. Pneumatization generally progresses from anterior to posterior and inferior to superior. In a CT-based study, volumetric analysis of the sphenoid sinus across a wide range of ages found that the average sphenoid sinus volume among children <4 years old was 0–1 cm^3, among

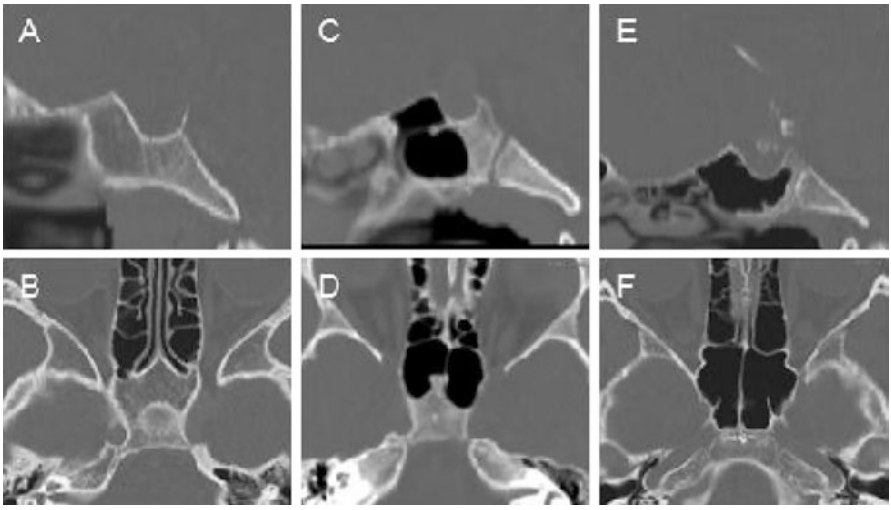

Fig. 28.1 Variations in sphenoid sinus aeration in children (**a**, **b**) Sagittal and axial CT views of conchal sphenoid sinus in a 15 year old with craniopharyngioma (**c**, **d**) Sagittal and axial CT views of presellar sphenoid sinus in a five year old with GH-secreting pituitary adenoma (**e**, **f**) Sagittal and axial CT views of sellar sphenoid sinus in a 13 year old with craniopharyngioma

those 5–9 years old 1–2 cm^3, and among those 10–14 years old 4–6 cm^3. There is a tendency to have a higher variability in the volume of the sphenoid sinus among adolescents. There are no differences in sphenoid sinus size between boys and girls.

Similar trends in sphenoid sinus pneumatization were seen in large patient samples using MRI. Jang et al. found that all patients studied had sphenoid aeration by three years of age and some subjects showed evidence of sphenoid development as early as two to four months of age [3]. Reittner et al. similarly retrospectively reviewed MRIs of 800 children and found evidence of pneumatization of the sphenoid in 19% of patients at age 12–15 months with complete pneumatization seen in all patients older than 10 [4].

Without complete pneumatization, identification of the carotid protuberances and opticocarotid recesses could be difficult. In these circumstances, neuronavigation is recommended, since patients with a conchal sphenoid sinus may have a reduced intercarotid distance. Neuronavigation can include frameless systems or intraoperative CT or MRI.

Endoscopic endonasal transsphenoidal surgery may have some theoretical benefits over microscopic transseptal or sublabial surgery in children with small nasal apertures since the endoscope can provide superior lighting and dynamic visualization. Concerns regarding instrument angles and working corridors with the endoscope can be mitigated by resecting the middle turbinate to accommodate a wider working channel.

Pituitary Adenomas

Overall, pituitary adenomas are uncommon in pediatric populations; however, the incidence increases with age such that they are more common in adolescents. Among pituitary adenomas in children, prolactinomas are most common followed by Adrenocorticotrophic Hormone (ACTH)-secreting adenomas and growth-hormone secreting adenomas. Nonfunctioning pituitary adenomas are less common. Although many of the clinical symptoms and presentations for hormone-active adenomas are similar between adults and children, there are some important distinctions, particularly with pediatric Cushing's disease and Growth Hormone (GH)-secreting tumors.

Prolactinomas

In both children and adults the presentation of prolactin-secreting pituitary adenomas varies based on the sex of the patient. In female adolescents, prolactinomas often present with headache, growth arrest, amenorrhea, and galactorrhea. In prepubescent girls, symptoms include delayed puberty, hypogonadotropic hypogonadism, and galactorrhea. Among boys, hyperprolactinemia secondary to prolactin-secreting adenoma presents with headaches, gynecomastia, and delayed puberty. Interestingly, boys may have a higher rate of harboring macroadenomas than girls.

As with adults, the first-line treatment for prolactinomas is a dopamine agonist. If symptoms persist or patients become intolerant to the side effects, then transsphenoidal surgery is indicated with the goal of complete adenectomy. Surgical remission can frequently be achieved in patients harboring microadenomas contained within the sella; however, there is a higher risk for incomplete surgical resection in macroadenomas and invasive tumors with parasellar extension. In these circumstances, surgical debulking can be performed to reduce adenoma burden for either further medical or radiosurgical treatment.

The evidence for surgical outcomes for pediatric prolactinomas is based on retrospective case series (evidence level 4). Recently, Liu et al. reported on nine patients under the age of 14 who had undergone transsphenoidal surgery for prolactinomas. Six patients were medication free postoperatively, and three patients with giant adenomas had incomplete resections. One patient underwent radiotherapy [6]. Partington et al. reported on 15 pediatric patients with prolactinomas. Eleven patients received grossly total resections, and four patients had subtotal resections secondary to parasellar extension. Five patients received radiotherapy, and no patient with microadenomas required postoperative adjuvant treatment [7].

Kane et al. studied the postoperative results of 56 children with non-ACTH-secreting pituitary adenomas. Forty-one patients had prolactinomas and eight patients had Prolactin (PRL) and GH adenomas. After transsphenoidal surgery, 70% of patients with microadenomas were in remission with a 25% recurrence rate, and patients with macroadenomas had a 33% remission rate with an overall remission rate of 55% including secondary treatments [8].

Tarapore et al. studied 32 pediatric patients with pituitary tumors. Twenty-one patients had prolactinomas. Fourteen patients had normalization of hormone levels with surgery alone, and an additional five patients had normalization with surgery and adjuvant treatments. Two patients had persistent hyperprolactinemia. Mindermann and Wilson also reported an 82% overall remission rate following surgery at long-term follow-up for prolactinomas [9].

Pediatric Cushing's Disease

ACTH-secreting adenomas causing Cushing's disease are rarely encountered in pediatric patients; however, they represent the second most common pituitary adenoma among prepubescent children. Unlike adult Cushing's disease, where there is a strong female predominance, Cushing's disease affects prepubertal boys and girls at an equal rate. Furthermore, the clinical presentation is different. Whereas adults present with abdominal obesity, hypertension, and diabetes, children additionally present with loss of linear growth and delayed puberty [10, 11].

Transsphenoidal surgery and selective adenectomy is the first-line treatment for Cushing's disease in children and adults [12]. Successful surgical resection results in immediate remission of hypercortisolemia while often maintaining normal pituitary function [13, 14]. Among pediatric patients with Cushing's disease, a majority present with microadenomas within the anterior pituitary gland [10, 15–19]. In patients where

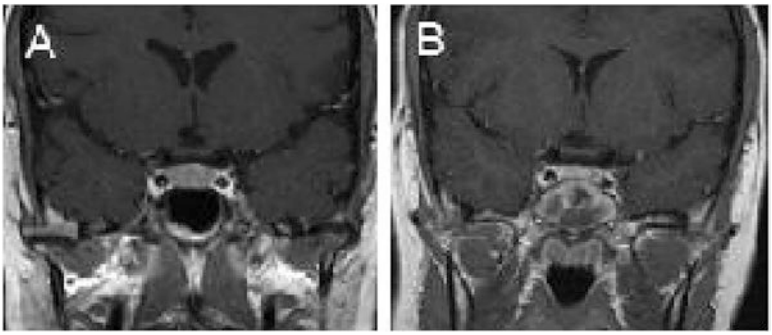

Fig. 28.2 MRI-negative Cushing's disease (**a**) Coronal postcontrast MRI showing normal pituitary imaging without evidence of ACTH-secreting adenoma in a 14-year-old girl (**b**) Coronal postcontrast MRI showing two-month postoperative scan following successful endoscopic transsphenoidal surgery for pituitary exploration and bilateral hypophysectomy; an ACTH-secreting adenoma was identified and removed on the right lateral border of the normal gland and remission was achieved

Cushing's disease is strongly suspected, but preoperative MRI is negative, inferior petrosal sinus sampling is useful to confirm the diagnosis (Fig. 28.2).

In the largest treated series of pediatric Cushing's disease reported, Lonser et al. presented 200 cases treated at the National Institute of Health. They found that transsphenoidal surgery was successful in achieving remission in 98% of patients initially and 93% at last follow-up (> than 1 year). Long-term remission was associated with younger age, microadenoma, and lack of adenoma invasion to the dura and cavernous sinus [10].

Storr et al. reported on 41 patients with Cushing's disease and found a male predominance, mostly microadenomas (with high rate of MRI negative imaging), and an early remission rate of 69% [11]. Devoe et al. reported an 83% initial remission rate among 42 children with a long-term remission rate of 73% [15]. In 2005, Kanter et al. reported the results for transsphenoidal surgery in a cohort of 33 pediatric patients. In this study, the authors reported a 76% remission rate with transsphenoidal surgery alone. Three patients had disease recurrence at long-term follow-up (18–92 months) and were treated successfully with repeat transsphenoidal surgery [16]. Savage et al. reported on 16 pediatric patients who had undergone transsphenoidal surgery for Cushing's disease. Seven had cortisol levels <50 nmol/l and two had cortisol levels <300 nmol/l. Seven patients underwent pituitary radiation [18].

Growth Hormone Secreting Tumors

Growth hormone-secreting pituitary adenomas are rare in children and adolescents. Among children whom epiphyseal growth plates have not fused, these tumors cause pituitary gigantism characterized by accelerated linear growth rates [20]. In adolescents, where growth plates have already fused, GH-secreting tumors cause classic

symptoms of adult acromegaly with enlargement of the frontal boss, large hands/feet, enlargement of the tongue, prominent jaw, and diabetes mellitus. Pituitary gigantism and adolescent acromegaly are associated with a number of genetic disorders including multiple endocrine neoplasia type 1, McCune–Albright Syndrome, neurofibromatosis type 1, Carney complex, isolated familial somatotropinomas, and X-linked acrogiganitsm [20].

As with pediatric Cushing's disease, surgical removal of the adenoma is considered the first-line treatment, although several medications including somatostatin analogues, GH-receptor antagonists, and dopamine agonists have shown promise in normalizing GH and IGF-1 levels. Since GH-secreting adenomas are so uncommon among children, many of the treatment algorithms are extracted from adult studies in acromegaly.

There are few series describing the surgical outcomes of GH-secreting adenomas in children [8, 21, 22]. In general, surgery is most successful among children with microadenomas confined to the sella. Complete surgical resection and normalization of GH levels is more difficult among patients with macroadenomas and tumors that have invaded surrounding structures. In fact, a higher proportion of children harboring GH-secreting adenomas have macroadenomas compared to those with Cushing's disease in whom microadenomas are more common. Thus, surgery alone is less successful in achieving disease remission, and adjuvant medical and radiotherapy is often necessary [8] (Fig. 28.3).

Abe et al. described the surgical results among 15 children (age <19 years) with GH-secreting adenomas. Four patients had microadenomas, 11 patients had macroadenomas, and tumor invasion of the cavernous sinus was seen in 40%. Grossly total adenoma resection was achieved in nine patients, and tumor recurrence was seen in two patients at long-term follow-up [21]. Creo et al. reported a series of 12 patients with GH adenomas treated with transsphenoidal surgery. Surgical remission was achieved in three of the 12 patients. The remaining patients were treated with medical therapy and radiosurgery [22].

Craniopharyngioma

In children, craniopharyngiomas (CP) represent 10% of intracranial tumors and are the most common sellar/parasellar tumors. CP are thought to be derived from persistent Rathke's pouch, and approximately half are diagnosed during childhood. Although CP are histologically benign tumors (WHO grade I), they can present significant treatment challenges. CP arise from the midline of the middle cranial fossa and commonly presents as suprasellar masses; however, some are purely intrasellar and others extend to the third ventricle or lateral middle fossa (Fig. 28.4).

Over the past two decades, the surgical paradigm for CP has evolved significantly. Given their high rate of recurrence, some experts advocate for complete resection [23]. However complete resection is associated with higher surgical morbidity, particularly in regard to postoperative hypothalamic dysfunction and poor postoperative quality of life [24]. Current surgical recommendations for CP involve

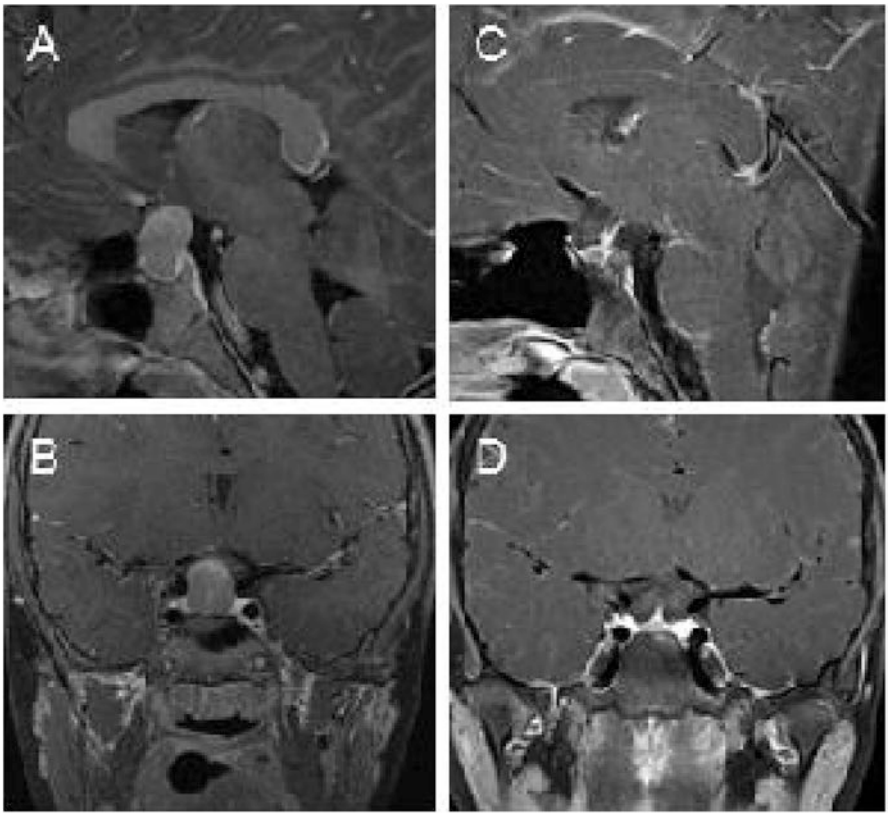

Fig. 28.3 GH-secreting macroadenoma (**a**, **b**) Sagittal and coronal postcontrast imaging demonstrating a GH-secreting macroadenoma with suprasellar extension in a five-year-old girl who presented with gigantism. (**c**, **d**) Sagittal and coronal postcontrast MRI 1 y after undergoing successful adenectomy with endoscopic endonasal transsphenoidal surgery

case-by-case analysis regarding surgical approach and extent of resection, ranging from complete resection to simple biopsy depending on location and projected surgical complications [25, 26].

For patients whose CP is contained within the sella or suprasellar/infrachiasmic extension, many experts advocate transsphenoidal surgery. In patients with CP involving the third ventricle and hypothalamus with retrochiasmatic extension transcranial surgery may provide improved access and control of critical neurovascular structures. Although histologically benign, CP are often adherent to surrounding structures, and complete resection risks compromising critical structures, which can result in morbidity for children.

Several groups have reported small case series using transsphenoidal approaches for pediatric CP. Initial reports primarily focused on using transsphenoidal approaches in pediatric patients with intrasellar or infradiaphragmatic tumor locations. In 1999, Abe et al. reported a series of 11 patients with infradiaphragmatic CP

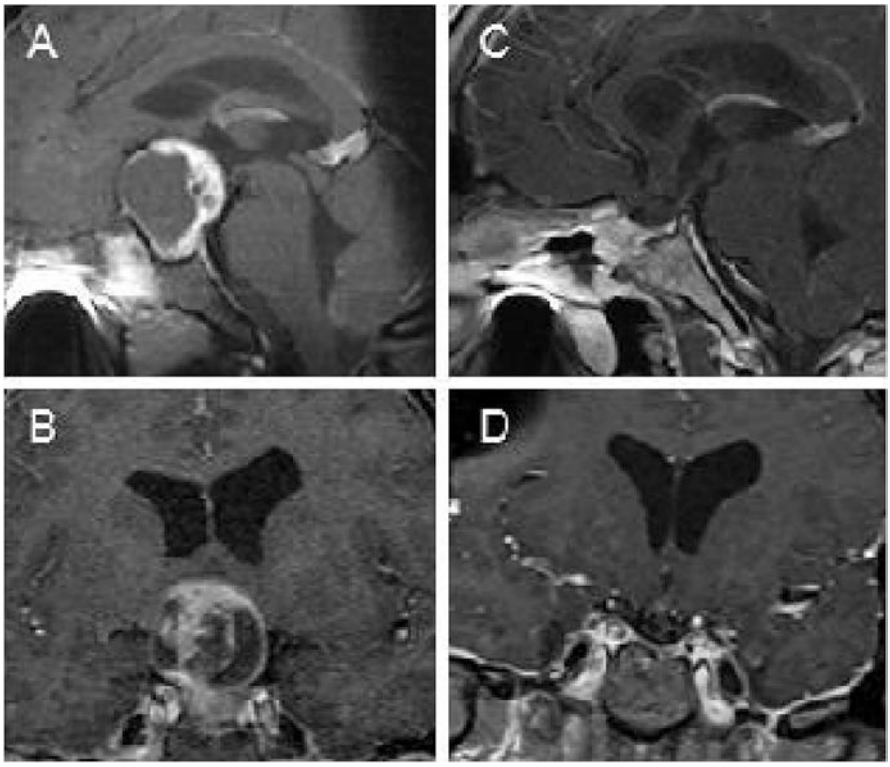

Fig. 28.4 Adamantinomatous craniopharyngioma (**a**, **b**) Sagittal and coronal postcontrast imaging demonstrating a cystic craniopharyngioma with suprasellar extension in a 15-year-old girl who presented with profound visual loss (**c**, **d**) Sagittal and coronal postcontrast MRI 3 y after undergoing endoscopic endonasal transsphenoidal surgery with complete resection

in children with 1-y follow up. In this series, three (27%) patients received grossly total resections while eight (73%) received subtotal resections [27]. In 2003, Im et al. reported surgical results from six children with CP. All patients in this study had sellar or infradiaphragmatic tumors; however, the authors noted that most of these tumors had large suprasellar extensions. Complete resection was obtained in all patients, and the authors advocated that transsphenoidal surgery was a good indication for select patients with CP [28].

In 2010, Jane et al. reported on a series of 22 patients with infradiaphragmatic CP who had undergone either primary transsphenoidal surgery (11 patients) or transsphenoidal surgery after a prior transcranial approach (11 patients). Among the whole cohort of patients, a grossly total resection was achieved in 15 patients (68%), and a radical subtotal resection was performed in four patients (22%). Patients with recurrent tumors were less likely to experience a gross total resection. At distant follow-up with a mean time of 82 months, there was an 18% recurrence rate. Patients who received subtotal resections were much more likely to have recurrences than those who received gross total resection [29].

More recently, Sankhla et al. reported a series of 15 pediatric patients with supradiaphragmatic (retrochiasmatic) CP treated by extended endonasal transsphenoidal surgery. Ten patients (67%) in this series had either gross total or near-total resections and four patients (27%) had subtotal resections. The authors concluded that with advances in endoscopic transsphenoidal surgery and skull-base reconstruction, this approach is a viable option for many cases of pediatric CP [30]. Koutourousiou et al. reported on 64 patients with craniopharyngioma treated with endoscopic transsphenoidal surgery including patients with suprasellar and supradiaphragmatic extension (17 patients were children). In this study the authors noted an overall surgical success rate of 72% (greater than 95% tumor resection). Overall recurrence was noted in 34% of patients throughout the study duration [31]. Among children who presented without endocrinopathy, all patients required some form of hormone replacement. The authors noted that despite a higher rate of surgical success for pediatric patients, there was a higher rate for recurrence. Importantly, Koutourousious et al. noted that when CP presents with some form of sellar extension or expansion of the sella, there is a natural surgical corridor to supradiaphragmatic tumors that can be accessible through a transsphenoidal corridor [31].

Complications from Transsphenoidal Surgery

The complications of transsphenoidal surgery include surgical morbidity related to the procedure (CSF rhinorrhea), endocrinological complications, and disease persistence/recurrence. In general, postoperative cerebrospinal fluid (CSF) rhinorrhea is a complication occurring in 3–15% of most adult series. These rates are comparable among pediatric transsphenoidal series as well. Kassan et al. reported CSF leak in two patients (8%) [32], and Locatelli et al. reported three CSF leaks among a cohort of 27 patients [33]. Postoperative CSF rhinorrhea predisposes patients to meningitis, and is treated with either repeat transsphenoidal surgery with sellar reconstruction and/or temporary CSF diversion (e.g., via a lumbar drain or external ventricular drain). Postoperative CSF rhinorrhea can usually be managed without significant additional surgical morbidity; however, it does contribute to extended length of hospitalization and the cost of additional surgical procedures.

CSF rhinorrhea rates are higher in endoscopic transsphenoidal surgery series for patients with CP with reports ranging from 0% to 58% [25, 26, 28–31]. Tumor size and location are likely contributors to this observation. However, more recent studies have reported lower rates with the common use of vascularized nasal-septal mucosal grafts for sellar reconstruction.

Surgical injury of the internal carotid artery is a rare, but potentially morbid, complication. Kanter et al. reported a single vascular injury among their series in Cushing's disease which did not require any further treatment and did not result in any new neurological deficits [16]. Lonser et al. reported sinus fractures in two patients who had undergone sublabial, microscopic approaches for Cushing's disease, which was caused by overdistraction of the nasal speculum [10]. Overall, the procedural morbidity for transsphenoidal surgery is low.

Postoperative endocrinological complications include diabetes insipidus, new anterior pituitary dysfunction (hypocortisolemia, hypothyroid), and syndrome of inappropriate anti-diuretic hormone (SIADH). Among children treated for pituitary adenomas, reported rates of endocrinological complications are similar after transsphenoidal surgery for adults. The risk factors for developing new endocrinological deficits among children have not been well defined; however, patients with preexisting endocrinopathies may have a higher risk for new endocrinological dysfunction, and patients with large or invasive tumors may be more likely to require postoperative hormone replacement. Presumably, this is secondary to compression of the normal pituitary gland and manipulation of the gland during adenoma dissection. Patients with new endocrinological dysfunction should be evaluated and treated by an endocrinologist for proper hormone replacement.

Among patients with prolactinomas, Liu et al. reported five (56%) patients had electrolyte disturbances, two (22%) patients had diabetes insipidus, and two (22%) had hypothyroidism [6]. Coloa et al. reported persistent GH deficiency among four of 26 patients after surgery for prolactinomas [34]. In patients with Cushing's disease, Devoe reported 25% of patients had hypothyroidism, 20% had GH deficiency, and 10% required hydrocortisone replacement therapy [15]. Abe et al. reported a 20% rate of diabetes insipidus among patients treated for GH-secreting adenomas [21].

Some pediatric patients with craniopharyngioma present preoperative endocrine deficits. However, most series report a relatively high rate of new postoperative panhypopituitarism after either transcranial or transsphenoidal surgery. Im et al. reported that all patients treated with radial resection via a transsphenoidal approach for CP had new hypopituitarism [28]. Jane et al. reported a 67% rate of hypopituitarism and 37% rate of new obesity among children treated for CP [29].

Disease persistence and recurrence are relatively common outcomes from hormone-active pituitary adenomas and craniopharyngioma. Among pituitary adenomas, persistent/recurrent disease is caused by microscopic or gross residual tumor [12, 35]. In patients who fail to achieve initial disease remission, early surgery may be indicated if the surgeon believes that a complete tumor resection is achievable. This may not be feasible in patients with extremely large or invasive tumors, and adjuvant medical and radiotherapy may be indicated. Late disease recurrence typically occurs within 5 years of surgery, but in some cases can be much longer. Recurrent hormone-active pituitary tumors can be treated with further surgery, medical therapy, radiotherapy, or some combination thereof.

Long-term follow-up of among pediatric patients with pituitary adenomas invariably demonstrates a considerable rate of disease recurrence. Among patients with Cushing's disease, Devoe et al. reported relapse in seven patients an average of 4.2 y after surgery [15], and Lonser et al. reported 14 patients with disease recurrence an average of 4.7 y after surgery [10]. Alexandraki et al. reported 22.7% recurrence rate for microadenomas and a 33% rate for patients with macroadenomas in patients with Cushing's disease [36]. Among patients with non-ACTH-secreting adenomas Kane et al. reported a 25% recurrence rate in patients with microadenomas and a 33% recurrence rate among patients with macroadenomas [8].

Conclusions

Pediatric pituitary tumors are uncommon, and they require careful evaluation and treatment for optimal outcomes. Among pediatric pituitary adenomas, hormone-secreting tumors are more common than nonfunctioning tumors and can have differing clinical presentations compared to adults. Transsphenoidal surgery is indicated as a first-line treatment for medication-resistant prolactinomas, ACTH adenomas, and GH adenomas. Surgery is frequently successful in achieving disease remission and maintaining normal pituitary function, and surgical treatment failures or disease recurrence can be treated with repeat surgery or radiosurgery. Craniopharyngioma is the most common parasellar tumor in children. Transsphenoidal surgery for craniopharyngioma is becoming an increasingly popular approach, particularly for tumors with sellar origin or extension and can be safely used in children with significant suprasellar extension. Overall, transsphenoidal surgery is safe to perform in children. Complications from transsphenoidal surgery include CSF rhinorrhea, new hypopituitarism, and disease recurrence.

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Pituitary Apoplexy

29

Patrick M. Flanigan, Arman Jahangiri, Han S. Lee, and Manish K. Aghi

Introduction

Apoplexy is derived from the Greek word "apoplĕxía" meaning "struck down by violence", which aptly emphasizes the acute and sometimes life-threatening nature of pituitary apoplexy [1]. Pituitary apoplexy is the clinical syndrome that usually arises from hemorrhage and/or infarction of a pre-existing pituitary adenoma. It was first described by Pearce Bailey in 1898 in a man with acromegaly who presented with sudden headache, fever, vomiting, visual loss, and ophthalmoplegia [2, 3]. However, it was not until 1950 that clinicopathologic examination of five patients who had rapid death secondary to pituitary hemorrhage and/or widespread necrosis allowed Brougham, Heusner, and Adams to definitively coin the term "pituitary apoplexy" [4].

Pituitary apoplexy arises from hemorrhage, hemorrhagic infarction, and/or ischemic infarction in the setting of a pituitary adenoma. The majority of cases of pituitary apoplexy occur into pituitary adenomas; however, pituitary apoplexy can occur in sellar adenoma, sellar tuberculoma, craniopharyngioma, Rathke's cleft cysts, hypophysitis, and pituitary metastasis [5–8]. Whereas Sheehan's syndrome, ischemic necrosis of the pituitary gland secondary to excess intrapartum hemorrhage, is considered a condition distinct from pituitary apoplexy [9].

Pituitary apoplexy can have devastating consequences [5]. The rapid increase in sellar tissue volume and intrasellar pressure that characterizes pituitary apoplexy can cause a variety of impairments, such as blindness, ocular palsy, and worsened

Patrick M. Flanigan and Arman Jahangiri contributed equally to this work.

P.M. Flanigan, BS
Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA

A. Jahangiri, BS • H.S. Lee, MD, PhD • M.K. Aghi, MD, PhD (✉)
University of California at San Francisco, Neurological Surgery, San Francisco, CA, USA
e-mail: Manish.Aghi@ucsf.edu

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_29

pituitary function, due to mass effect on nearby structures. Outcome of pituitary apoplexy is highly variable; pituitary apoplexy results in lasting deficits in some cases while other patients make a complete recovery. Accordingly, optimal management of pituitary apoplexy in less symptomatic patients is controversial. While prompt surgical decompression is indicated in most cases, conservative management is sometimes adopted for selected patients with normal consciousness and without visual acuity deficits. Overall, pituitary apoplexy is best managed through a combination of acute neurosurgical evaluation and timely surgical intervention if needed as well as a multidisciplinary approach involving ongoing input from neurosurgical and endocrine services. With these points in mind, here we discuss the epidemiology, pathophysiology, risk factors, and management of pituitary apoplexy.

Epidemiology

It is difficult to ascertain the true incidence of pituitary apoplexy due to its rarity. The reported incidence of pituitary apoplexy ranges between 0.6% and 26% of all adenoma cases [7, 10–15]. A large study conducted in the UK estimated the incidence of pituitary apoplexy at 0.17 episodes per 100,000 person-years and the prevalence at 6.2 cases per 100,000 inhabitants [5]. Importantly, cases of pituitary apoplexy occur four times as often in undiagnosed pituitary adenomas compared to in diagnosed pituitary adenomas [16], underscoring the benefit of timely diagnosis and treatment of pituitary adenomas, which would prevent apoplexy in some of these patients.

Pituitary apoplexy seems to be more common in nonfunctional pituitary adenomas (NFPAs) than other tumor types. While NFPAs account for less than 40% of pituitary adenomas, they are the pre-existing tumor in 45%–82% of cases of pituitary apoplexy [12, 13, 17–20]. However, it has been proposed that acute damage that occurs during the apoplectic event might preclude detection of the functional status of a pituitary adenoma via retrospective histopathological and endocrine evaluations; this would lead to an overestimation of the proportion of pituitary apoplexy cases caused by NFPAs [21]. Prolactinomas and growth-hormone secreting tumors account for 5.5%–31% and 7.2%–25% of cases of pituitary apoplexy, respectively [7, 22–24]. Males are 1.5–2 times as likely to develop pituitary apoplexy [7, 13, 18, 22], and the mean age of diagnosis of pituitary apoplexy is 51 years [21, 25]. Pituitary apoplexy is quite rare in pediatric patients, which mirrors the rarity of pituitary adenomas in general within this patient population [26].

Etiology and Pathophysiology

Pituitary apoplexy occurs within the lesion itself, but can also involve normal pituitary gland [16, 27]. While commonly associated with hemorrhage, not all cases of apoplexy are hemorrhagic. In a series of 36 patients with histologically confirmed pituitary apoplexy, it was demonstrated that in 17 patients there was no evidence of hemorrhage, whereas in the other 19 there was hemorrhagic infarction or

hemorrhage alone [28]. Current research suggests that, in general, patients who have a pituitary infarction without a hemorrhagic component have less severe symptoms and a longer clinical course before seeking medical care than patients with pituitary hemorrhage or hemorrhagic infarction [17]. While the pathophysiologic basis of pituitary apoplexy is not completely understood, three main factors are thought to contribute to its development: outgrowth of vascular supply, compression of local vascular structures, and intrinsic abnormalities of the tumor vasculature.

First, rapidly growing adenomas are thought to outgrow their vascular supply, which leads to ischemia and necrosis of the tumor. This is consistent with the observation that macroadenomas are at a much higher risk than microadenomas for pituitary apoplexy [23, 24, 29]. Thus, it has been proposed that microadenomas probably undergo pituitary apoplexy via different mechanisms than macroadenomas, although the relationship between adenoma size and propensity for apoplexy is not well understood [21, 30, 31].

Second, large pituitary adenomas growing within the narrow space between the pituitary stalk and diaphragma sellae can lead to impingement of the local blood vessels such as the superior pituitary or infundibular vessels; this leads to ischemia, necrosis, and hemorrhage on the anterior lobe and tumor tissue [27].

Third, structurally and functionally abnormal vessels that are present within the adenoma might be prone to hemorrhage. Vessels within pituitary adenomas have been described as immature and poorly fenestrated with fragmented or ruptured basement membranes [32]. However, discovery of a molecular basis for the predisposition of some vessels of pituitary adenomas toward hemorrhage remains elusory. The role of VEGF in pituitary adenomas is controversial as VEGF levels are usually decreased in pituitary adenomas compared to normal pituitary gland [33–35]. However, some studies have reported that higher VEGF expression in pituitary adenomas correlates with higher likelihood of hemorrhage, while others found no such association [36–39]. Furthermore, one study proposed that TNFα induces MMP-9 and VEGF in pituitary adenomas, which may promote vascular hyperpermeability with microvessel dilation, leading to their hemorrhagic transformation [36–39].

The three aforementioned ways by which an adenoma could precipitate pituitary apoplexy are not mutually exclusive and may co-occur and interact.

Precipitating Factors

Also influencing the development of pituitary apoplexy are precipitating factors (Table 29.1). Although precipitating factors are important to note because they can aid in diagnosis and give clues about the etiology of pituitary apoplexy, which could prevent cases of apoplexy from occurring, it should be emphasized that pituitary apoplexy occurs without an identifiable precipitant in 60%–80% of cases [40, 41].

Many of the precipitating factors associated with pituitary apoplexy arise from patient diseases or treatments that cause damage to the vasculature of pituitary adenomas, eventually culminating in an acute hemorrhagic event. For example, direct damage can be caused by systemic arterial hypertension, fluctuations in arterial pressure, or diabetes mellitus [12, 19, 23, 42, 43]. Head trauma has also been associated

Table 29.1 Selected examples of factors precipitating pituitary apoplexy

Precipitating factors of pituitary apoplexy with supportive references
Arterial hypertension [12, 19, 23, 42]
Diabetes mellitus [43]
Trauma [44, 45]
Anticoagulant and antithrombotic medications [15, 19, 46–48]
Major surgery (e.g. cardiac surgery) [49–52]
Radiotherapy [53]
Hormonal hypothalamic-pituitary axis function assessment [54–58]
Somatostatin analogue administration [61]
Pregnancy [63, 64]
Cavernous sinus invasion [65]

with pituitary apoplexy, especially in those tumors with suprasellar extension, the proposed mechanism being shear force applied at the intrasellar-suprasellar junction leading to contusion and subsequent hemorrhagic infarction [44, 45].

Diagnostic evaluation and therapeutic management of pituitary tumors can also be precipitating factors for apoplexy. Anticoagulant and antithrombotic therapy may contribute to the development of pituitary apoplexy by increasing the likelihood for hemorrhage of pituitary adenoma vasculature [15, 19, 46–48]. A number of surgical procedures, such as cardiac surgery, can serve as risk factors for pituitary apoplexy since patients are exposed to fluctuations in operative blood pressure [49–52]. Radiotherapy is thought to precipitate apoplexy in those tumors with cystic portions compressing solid portions causing ischemia and hypoxia, which makes the tumor more likely to undergo hemorrhagic transformation when radiotherapy is administered [53]. Dynamic hormone testing with thyrotropin-releasing hormone (TRH) and gonadotropin-releasing hormone (GnRH) has also been associated with pituitary apoplexy, although this type of testing is not typically a component of the current routine assessment of hypothalamic-pituitary axis function [54–58]. The exact mechanisms by which these tests can precipitate pituitary apoplexy are not known. It has been proposed that TRH can elevate serum norepinephrine, which predisposes toward vasospasm or vasoconstriction of intratumoral blood vessels while GnRH is hypothesized to increase tumoral metabolic activity to such an extent that a vascular accident ensues [54, 59]. Additionally, somatostatin analogue administration might predispose toward apoplexy via a rapid decrease in tumor volume and somatostatin-mediated inhibition of angiogenesis could potentiate necrotic and hemorrhage transformation of the tumor in patients at risk for bleeding [60–62]. During pregnancy, anatomical and physiological changes to the pituitary gland occur such as lactotroph hyperplasia; this leads to enlargement of the pituitary gland, which is thought to predispose toward pituitary apoplexy in pregnant women with pituitary adenomas [63, 64]. One tumor-specific risk factor for pituitary apoplexy is cavernous sinus invasion. Cavernous sinus invasion is thought to correspond with more aggressive tumors and might predispose toward apoplexy via disruption of venous drainage of the tumor causing hemorrhage infarction [65].

In addition to medical factors, socioeconomics elements have recently been shown to serve as additional risk factors for pituitary apoplexy. Jahangiri et al. (2013) found that lack of a primary care physician and lack of health insurance were both significantly associated with pituitary apoplexy [66]. Poorer patients and non-Caucasians were more likely to prolong the time to seek medical care for adenoma-related symptoms and thus had a higher rate of apoplexy. Furthermore, pituitary apoplexy-associated visual symptoms in the elderly were often incorrectly attributed, either personally or by healthcare providers, to be secondary to aging, which also contributed to delayed diagnosis. Elderly patients, non-whites, and people of lower socioeconomic status are more likely to be afflicted with pituitary apoplexy and elderly patients have worsened outcomes when diagnosis is delayed.

Clinical Presentation

Regardless of the underlying pathophysiologic basis of pituitary apoplexy, clinical symptoms mostly arise from the anatomical compression of normal pituitary tissue and vital neighboring anatomical structures. Because a majority of the symptoms of pituitary apoplexy depend on the degree of pressure, symptoms can range from mild to severe; however, subclinical pituitary apoplexy is often considered a distinct entity [10, 67, 68]. The four most important clinical findings in pituitary apoplexy are headache, endocrine dysfunction, visual symptoms, and altered consciousness, which will be discussed in detail (Table 29.2).

Headache

The most common and the earliest symptom of pituitary apoplexy is headache, which is present in greater than 90% of cases [10, 69, 70]. Headache in pituitary apoplexy is severe, sudden, and unremitting in nature, often localizing to the

Table 29.2 Clinical manifestations of pituitary apoplexy

Clinical Finding	% of Patients	Comments
Headache [10, 69–71]	~ 90%	Commonly precedes other symptoms
Hypopituitarism [12, 14, 29, 81]	~ 80%	Corticotropic deficiency occurs in 70% of cases and hypopituitarism. Panhypopituitarism is more common than deficiency of a singular pituitary hormone.
Visual acuity decrease or visual field loss [12, 41, 69]	~ 70%	Associated with more severe cases of pituitary apoplexy
Ocular palsy [76]	~ 60%	Most common nerve affected is cranial nerve III
Alteration in consciousness [10, 11, 22]	~ 30%	Can be accompanied by stupor, lethargy, and, less commonly, coma

retro-orbital area, but can also present as bifrontal, and/or occipital [27]. Apoplexy patients are more likely to report headache as a symptom and tend to have a much shorter duration of headache before presentation compared to patients with other sellar lesions [71]. The pathogenesis of the headache in pituitary apoplexy is likely due to extravasation of blood, leading to meningeal irritation and/or dural traction from the local expansion [40].

Endocrine Dysfunction

The exact percentage of cases in which pituitary apoplexy causes hormonal deficiency is difficult to ascertain. As most patients who develop pituitary apoplexy harbor a pre-existing macroadenoma, it is possible that at least part of the hormonal deficiency detected at presentation with pituitary apoplexy is actually due to the compressive effects of the preceding macroadenoma. Nonetheless, deficiency in one or more of the anterior pituitary hormones is estimated to be present in about 80% of pituitary apoplexy patients [21]. Panhypopituitarism is more common than deficiency of a singular pituitary hormone [41].

Discussion of the blood supply to the pituitary is important for understanding a mechanism by which panhypopituitarism occurs in the setting of pituitary apoplexy. Normally, the anterior pituitary is supplied predominantly by the hypophyseal portal system, which receives its blood supply from the superior hypophyseal artery, while the posterior pituitary is supplied by the inferior hypophyseal artery [72]. MR enhancement studies indicate that pituitary adenomas, however, receive most of their vascular supply directly from the inferior hypophyseal artery. Tumor compression of the superior hypophyseal artery and its branches against the diaphragm sellae can impede blood supply to the normal tissue leading to ischemic necrosis of the gland. Also, the direct compression of the normal tissue by the adenoma decreases its perfusion pressure gradient, which also leads to ischemic necrosis of normal pituitary tissue thus causing panhypopituarism [23].

Corticotropic deficiency is the most life-threatening hormonal deficiency in pituitary apoplexy as it can lead to severe hemodynamic compromise and hyponatremia; adrenocorticotropic hormone (ACTH) deficiency occurs in about 70% of patients [73]. Deficiency in other anterior pituitary hormones is not as clinically alarming in emergent situations. For example, growth hormone (GH) deficiency has been reported to occur at approximately the same frequency as corticotropic deficiency; however, its values are not always measured [74]. Thyroid-stimulating hormone (TSH) deficiency occurs in about half of cases whereas gonadotropin deficiency occurs in about 75% of cases [73]. Less frequently, hypoprolactinemia, Syndrome of Inappropriate Antiduiretic Hormone secretion (SIADH), or diabetes insipidus may also occur, which may either serve as a presenting feature of pituitary apoplexy or manifest postoperatively.

Visual Symptoms

Visual symptoms in pituitary apoplexy are common and include visual field deficits, a decline in visual acuity, photophobia, and cranial nerve palsies. Visual deficits occur in 50%–82% of cases of pituitary apoplexy [10, 12, 14, 75]. The suprasellar extension of the expanding mass can compress the optic chiasm leading to the classical presentation of bitemporal hemianopsia. Ocular palsy occurs in more than half of patients with pituitary apoplexy [76]. Lateral extension of the mass compresses the cavernous sinus and can cause palsy of any of its nerves (III, IV, V1, V2, and VI). The third cranial nerve is the most commonly involved nerve in pituitary apoplexy likely due to its proximity to the sella; it is affected in up to 50% of cases of pituitary apoplexy [77]. With respect to outcome, apoplexy patients are less likely to experience postoperative improvement in visual symptoms compared to patients with visual symptoms arising from other pituitary lesions (53 vs. 81%) [66].

Altered Consciousness

In addition to visual symptoms, alteration of consciousness is another alarming clinical feature of pituitary apoplexy and one that favors the decision for immediate surgical decompression. Altered consciousness may be accompanied by stupor, lethargy, and less frequently, coma and occurs in about 30% of patients [10, 11, 22]. Altered consciousness is seen more frequently in those patients who have some of the medical risk factors mentioned earlier for the development of pituitary apoplexy (e.g. recent cardiac surgery, taking anticoagulant therapy) [16].

Other Findings

While the aforementioned clinical features are common and more defining of pituitary apoplexy, a variety of diverse symptoms can be seen as a result of pituitary apoplexy. In fact, as mentioned below, some of these symptoms (e.g. nuchal rigidity) can make it quite difficult to diagnose pituitary apoplexy due to the overlap with other conditions. Nonspecific symptoms of pituitary apoplexy can include nausea, nuchal rigidity, vomiting, and unexplained hyperpyrexia. Although rare, cerebral ischemia can result from compression of the internal carotid artery against the anterior clinoid or from its vasospasm secondary to subarachnoid hemorrhage, both of which require immediate neurosurgical intervention.

Differential Diagnosis

Pituitary apoplexy is sometimes a diagnostic challenge due to its rarity, the fact that it usually occurs in patients whose pituitary adenomas are undiagnosed, and it can mimic several different neurologic conditions. The symptoms and signs of pituitary

apoplexy can have significant overlap with aneurysmal subarachnoid hemorrhage (SAH), bacterial meningitis, acute hydrocephalus, migraine, cavernous sinus thrombosis, and midbrain infarction [41, 73]. The two most important differential diagnoses that should be considered for the clinical symptoms associated with pituitary apoplexy are bacterial meningitis and SAH, both of which can be distinguished from pituitary apoplexy via imaging [78, 79].

Radiologic Findings

Diagnosis of pituitary apoplexy relies on previously mentioned signs and symptoms of pituitary apoplexy together with either prior knowledge or discovery of a pituitary adenoma. Imaging studies used to make this diagnosis include computerized tomography (CT), magnetic resonance imaging (MRI), and magnetic resonance angiography in some cases. While MRI is superior to CT for the diagnosis of pituitary apoplexy, the majority of patients with pituitary apoplexy will initially undergo CT imaging in an emergency setting. In most cases, clinical suspicion before imaging favors a diagnosis other than pituitary apoplexy due to its rarity, which makes imaging of paramount importance in diagnosing this condition [80].

On CT, when pituitary apoplexy occurs due to hemorrhage, there is classically a hyperdense lesion inside the sella turcica with minimal contrast enhancement; however, the lesion becomes less hyperdense as it ages, which occurs in the days following the acute onset. Especially if imaged after the lesion has aged, MRI imaging is needed to differentiate this finding from other hyperdense lesions in the sellar and suprasellar region such as aneurysms, meningiomas, germinomas, and lymphomas [80]. Furthermore, the sensitivity of CT for the diagnosis of pituitary apoplexy is quite low, reported at below 50% [12, 29]. This is possibly due to decreased ability to distinguish degenerative and/or cystic changes inside a pituitary neoplasm from previous hemorrhage [28]. While CT cannot always distinguish between different lesions in the pituitary area, it is effective in detecting expansive pituitary lesions causing sellar enlargement in up to 94% of cases [10, 12, 75, 80]. The detection of a pituitary mass on CT is of particular diagnostic benefit for physicians during the acute phase to exclude subarachnoid hemorrhage in those patients presenting with severe headache.

Typically, CT scans should be supplemented with contrast-enhance MRI as long as it does not inappropriately delay neurosurgical intervention. MRI is superior to CT in identifying the presence of subacute hemorrhage/infarct with a sensitivity for detecting pituitary apoplexy of approximately 90% [81, 82]. The first blood component detectable by MRI is deoxyhemoglobin, thus MRI is most effective at detecting lesions greater than 24 h old. Depending on the age of the lesion, pituitary apoplexy appears differently on MRI. Subacute or chronic hemorrhage usually appears heterogenous due to the presence of blood products in various stages [80]. After contrast, a peripheral rim of enhancement on MRI is characteristic (Fig. 29.1). While not as pathognomonic, thickening of the sphenoid sinus mucosa in the acute

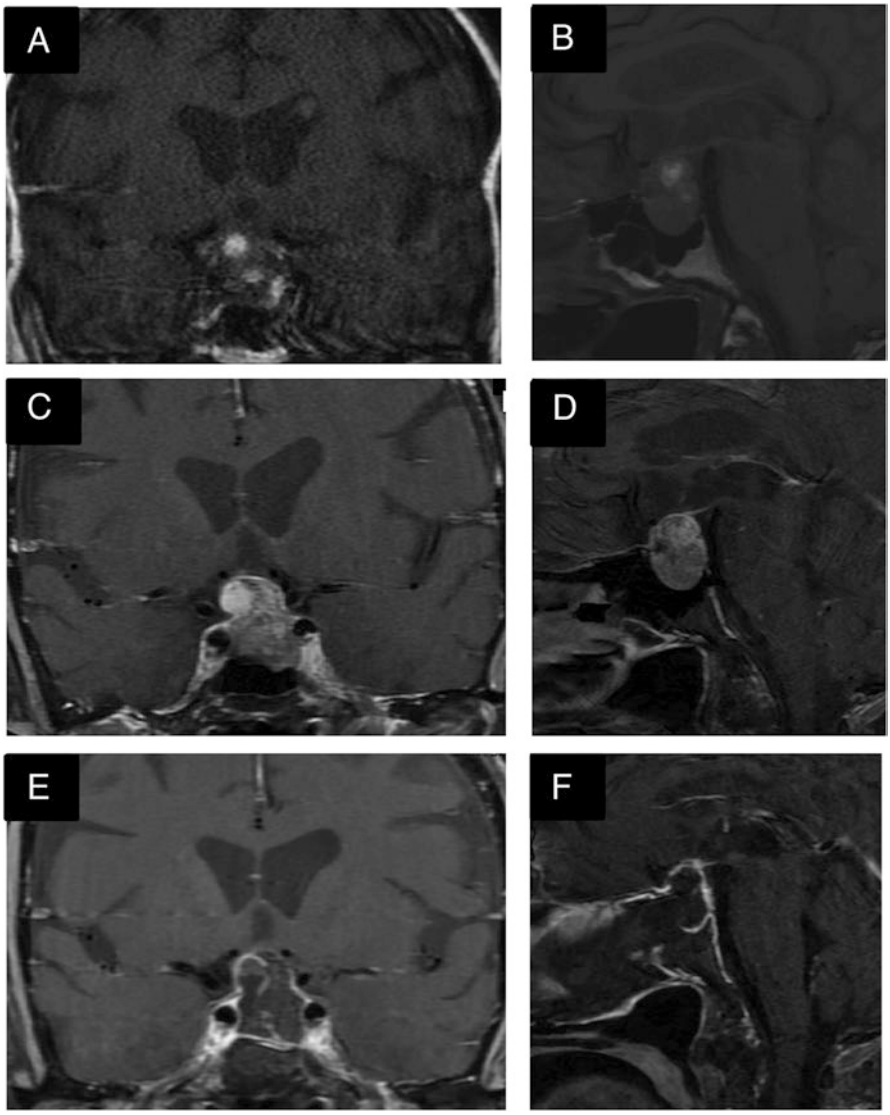

Fig. 29.1 Representative MRI of pituitary apoplexy. This 79-year-old male presented with acute decrease in visual acuity. (**a**, **b**) Pre-gadolinium preoperative coronal (A) and sagittal (B) MRI revealed T1 hyperintensity in the right suprasellar and left sellar regions suggestive of acute blood products. (**c**, **d**) Post-gadolinium enhancing preoperative coronal (**c**) and sagittal (**d**) MRI revealed a sellar lesion with suprasellar extension with the characteristic peripheral enhancement. (**e, f**) Immediate postoperative coronal (**e**) and sagittal (**f**) MRI revealed a complete resection with floppy folds of expanded diaphragma that had previously laid over the tumor and would be expected to fully collapse into the sella over the ensuing weeks

stages of apoplexy has been observed, and is possibly caused by venous congestion caused by obstruction of venous outflow secondary to the increased intrasellar pressure associated with apoplexy [83]. It has been determined that T2-weighted imaging (T2 W1) is best during the acute phase (0–7 days) showing hypointensity in the area of the lesion. In the subacute phase (7–21 days), the lesion appears hyperintense on T1-weighted imaging (T1 W1) as well as on T2 W1. In the chronic phase (>21 days), there is a strong hypointensity on both T1 W1 and T2 W1 [80]. MRI is also superior in providing more accurate depiction of adjacent anatomical structures, which is useful for determining extension of the tumor into structures such as the cavernous sinus. Although MRI is the most effective imaging modality for pituitary apoplexy, it is important to consider the limitations of CT, particularly its low sensitivity, as this is often the first scan patients receive in emergency settings. If the diagnosis of pituitary apoplexy is suspected, it is recommended that MRI scan of the pituitary gland be performed.

Management

The broadest division in the management of pituitary apoplexy is surgical versus conservative, both of which aim to decrease the compression in the sellar and suprasellar regions. Because this condition is rare and can have variable presentations and outcomes, the best management strategy for less symptomatic patients (i.e. no alteration in consciousness or visual changes) is not as defined. Regardless of the end decision, immediate administration of intravenous glucocorticoids is indicated when hypoadrenalism is confirmed or suspected as this hormone deficiency can result in significant morbidity if not treated promptly. High-dose glucocorticoids can also decrease inflammation, which can improve symptoms secondary to expansion of sellar contents [84]. Furthermore, if apoplexy symptoms are milder and the patient is clinically stable, serum prolactin should be measured as prolactinomas can become apoplectic and may be successfully treated with medical therapy [85]. Regardless of the type of intervention, most patients require postoperative supplementation with at least one hormone, most commonly thyroid hormone, after development of pituitary apoplexy [12, 13, 84]. All patients with pituitary apoplexy should receive long-term, multidisciplinary follow-up to manage hormonal levels and monitor for tumor recurrence.

Operative Management

Immediate surgical intervention is the standard of care for patients with acute loss of visual fields, severe decreases in visual acuity, and/or signs of brain compression. Surgery is typically performed through a transsphenoidal corridor achieved through a microscopic or endoscopic approach with a transition toward the latter approach occurring among neurosurgeons in recent years [40, 86]. The transsphenoidal approach allows for adequate decompression of optic pathways

and other neuroanatomical structures adjacent to the tumor, and it is generally safer than craniotomy. Not surprisingly, functional outcomes are worse for patients undergoing surgery for apoplexy than for patients undergoing surgery for non-apoplectic pituitary adenomas [15, 66]. In terms of timing, surgery as soon as possible and ideally within the first 24 h eliminates the possibility of symptoms worsening [87].

Is there a Role for Conservative Nonsurgical Management of Pituitary Apoplexy?

While pituitary apoplexy is generally best managed surgically in an urgent manner, there are scenarios where conservative nonsurgical management of pituitary apoplexy can be considered. For example, oculomotor palsies, which often reflect mass effect on the cavernous sinus from the intrasellar hematoma, can recover with nonsurgical management as the hematoma slowly reabsorbs, a premise first supported by a 1978 report of nine patients with apoplexy who experienced spontaneous recovery without surgical intervention [88]. A prospective study conducted by Maccagnan et al. (1995) evaluated the outcomes of 12 patients with pituitary apoplexy. All patients were initially treated conservatively using high-dose dexamethasone. Only five of the 12 patients eventually required surgery due to the lack of improvement in their consciousness and visual impairment [89]. This study reported similar outcomes between each groups with only one patient from each group experiencing recurrence of their adenoma. While logic would suggest that surgical management would decrease rates of tumor recurrence in pituitary apoplexy, one study suggested that the recurrence rate is about 10% in patients with pituitary apoplexy regardless of the type of management received [75]. Additionally, apoplexy of a hypersecreting tumor resolves hormonal hypersecretion in some of these patients, underscoring the importance of being cognizant that a patient might have had a hypersecreting tumor for cases where tissue is not obtained due to the lack of a surgical procedure; this suggests that resolution of hormonal hypersecretion is not necessarily an indication for surgery in apoplexy. Overall, while there is no evidence supporting nonsurgical management over surgical management, particularly by a neurosurgeon with sufficient pituitary surgery experience, there is at least some data suggesting that patients with comorbidities rendering surgery risky at their particular center or patients lacking access to neurosurgical care who have oculomotor palsies rather than optic nerve compression can be considered for nonsurgical management [41, 75].

Pathology

As mentioned previously, pituitary apoplexy can be divided into three pathological categories: infarction without hemorrhage, hemorrhage alone, or hemorrhagic infarction [28]. Once the pathologist has confirmed the presence of these features of apoplexy, the next question the pathologist addresses is whether or not the specimen has

viable tumor. It is possible that apoplexy patients with pathology specimens showing viable cells may need closer follow-up as their recurrence risk might be elevated compared to those with completely necrotic specimens; however, there are no studies to date investigating this premise. If there is viable adenoma in the specimen, the pathological considerations in patients with pituitary apoplexy are similar to those with pituitary adenomas. For example, the use of the MIB-1 antibody to detect the proliferative marker Ki-67 can provide useful information since adenomas with a higher proliferative index tend to be more invasive, which can lead to an increased chance of residual tumor that might not be detectable and postoperative imaging but could increase the risk of recurrence [90]. Close follow-up of patients with tumors showing this staining is recommended. The pathologist should also stain any viable tumor to ascertain staining of the specimen for the common hormonal stains ACTH, prolactin, and GH. Interpretation of these stains can be challenging as the quality of the specimen can create false negative stainings in apoplexy cases. If these stainings are positive, correlation with circulating hormone levels should be assessed. If systemic hormones are not elevated, there are two possible interpretations. First, the patient may have had a hypersecreting tumor whose infarction eliminated the hypersecretion. Alternatively, the patient may have had a silent hormonally positive tumor. Silent corticotropic pituitary adenomas, tumors with positive ACTH-staining, but without clinical or laboratory evidence of Cushing's disease, are believed to have higher rates of apoplexy (33% in one study) than other pituitary adenomas [91]. Close monitoring of silent corticotropic pituitary adenomas is paramount as these tumors have higher rates of recurrence and behave more aggressively in general [92]. (Fig. 29.2).

Postoperative Care

Close and frequent clinical examination in the immediate postoperative period (i.e. first 48 h) is imperative for patients undergoing surgery for pituitary apoplexy. Unlike patients undergoing elective resections of pituitary adenomas, most apoplexy patients have not had a full endocrine evaluation in the preoperative setting consequent to the emergent nature of their condition [84], so it is imperative to complete this evaluation upon completion of surgery, with the exception of assessing the adrenocortical axis, as patients should have been on stress dose steroids upon recognition of apoplexy by imaging, with tapering to maintenance steroids occurring after surgery. Patients should be closely monitored for potential complications of surgery including diabetes insipidus, vision loss, cortisol deficiency, meningitis, and cerebrospinal fluid leak [84, 93]. Diabetes insipidus is one of the most frequent complications of pituitary apoplexy, occurring in approximately 16% of patients in the postoperative in-hospital period [12]. Fluid balance should be monitored regularly during the first 48 h. Plasma electrolytes, plasma and urine osmolality, should be assessed in the first 48 h, preferably once daily. Patients should be assessed for visual improvement after surgery, which often occurs. Patients with visual deterioration beyond their preoperative level of visual decline or neurological deterioration should have an urgent CT scan, which can be followed by an MRI scan if the CT does not reveal a hematoma requiring a return to the operating room.

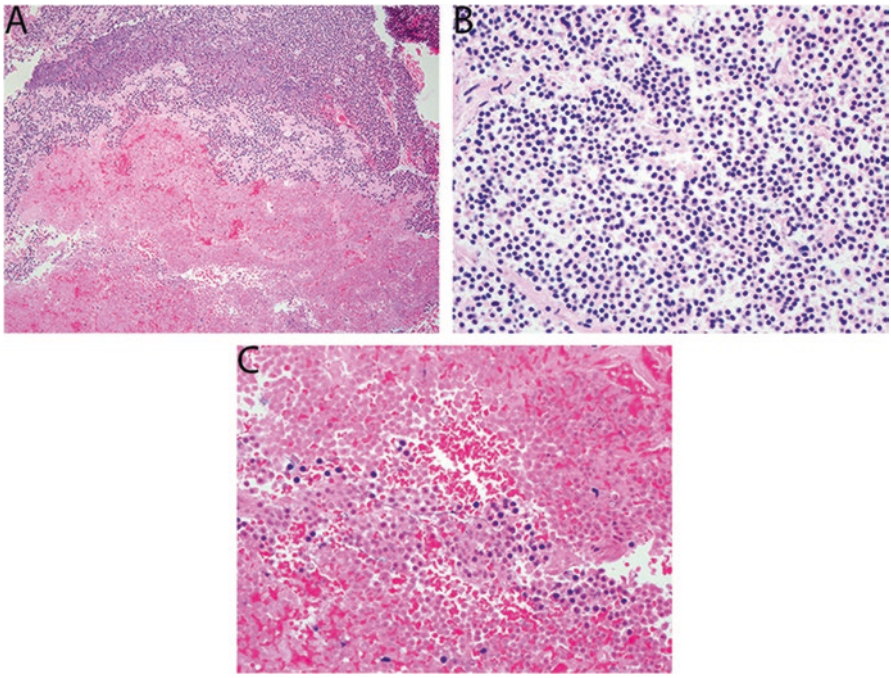

Fig. 29.2 Pathologic analysis of pituitary apoplexy. This 55-year old female presented with acute decrease in visual acuity and the following photomicrophaghs of a histopathological specimen obtained from the sella were produced: (**a**) H&E stain of the sellar tissue contained both hemorrhage and pituitary adenoma cells, 40x magnification. (**b**) H&E stain at higher power revealed homogenous nucleated neoplastic pituicytes, 160x magnification. (**c**) H&E stain at higher power revealed red (nonnucleated) cells interspersed with few pituicytes, consistent with hemorrhage, 160x magnification

Patients should be assessed in the outpatient setting 4–8 weeks after surgery. Pituitary function tests and cranial nerve examination should be performed. Thyroid function tests are especially important at this time, as they can be normal in the immediate postoperative period despite thyrotropic cell damage. Long-term follow-up for hormonal evaluation is indicated in all apoplexy patients. A baseline MRI is typically taken 3–6 months after surgery for apoplexy. Several studies recommend annual surveillance MRIs for the first 3–5 years after surgery for apoplexy and then every 2 or 3 years thereafter [84, 93].

Conclusions

Pituitary apoplexy is a syndrome that manifests as a result of hemorrhage and/or infarction of a pre-existing pituitary adenoma. The cause of pituitary apoplexy is unknown; however, several possibly co-occurring pathogenic mechanisms have been proposed, and identification of precipitating factors can serve to prevent some cases

from occurring. Pituitary apoplexy is best diagnosed via clinical suspicion followed by magnetic resonance imaging. Upon identification of apoplexy, prompt treatment to correct steroid deficiency is imperative. While urgent transsphenoidal surgery is the main treatment of apoplexy, particularly for patients with acute visual impairment and/or impaired consciousness, reports of favorable outcomes for patients with relatively preserved visual acuity and comorbidities precluding surgery that are treated conservatively should be acknowledged when counseling patients as to the various treatment alternatives. An intimate knowledge of the precipitating factors, clinical features, and management of pituitary apoplexy has the ability to improve patient outcomes.

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Anatomical Approaches to Giant Pituitary Tumors

30

André Beer-Furlan, Ralph Abi-Hachem, Ali O. Jamshidi, Ricardo L. Carrau, and Daniel M. Prevedello

Introduction

Although several definitions have been proposed, giant pituitary adenomas are most commonly defined in the literature as tumors 4 cm or greater in maximum diameter. They account for 5–14% of adenomas in surgical series, and pose a significant treatment challenge [1–3].

The tumor size, invasiveness, and irregular extension are the challenges involving the management of these pathologies, which often require more than one surgical approach or treatment modality. The degree of radical resection of giant adenomas is restricted to less than 50% in every published surgical study and is associated with a higher complication rate compared with non-giant pituitary adenomas [1–3]. Additional radiation therapy and medical therapy may be necessary to obtain long-term control of tumor growth [1, 3].

Several authors use the microscopic transsphenoidal or various frontal and frontotemporal transcranial routes as their choice for surgical management of giant pituitary adenomas [1, 2, 4, 5]. Endoscopic endonasal approaches have been used increasingly over the last decade for the treatment of many extended skull base tumors, including giant pituitary adenomas [6–8].

A. Beer-Furlan, MD • R. Abi-Hachem, MD • A.O. Jamshidi, MD • R.L. Carrau, MD
D.M. Prevedello, MD (✉)
The Ohio State University Wexner Medical Center, Department of Neurological Surgery, Columbus, OH, USA
e-mail: Daniel.Prevedello@osumc.edu

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_30

Surgical Goals and Preoperative Planning

Pituitary macroadenomas are a heterogeneous group of lesions. In cases of giant and invasive functioning pituitary adenomas, the chances of hormonal cure with surgery alone are low. The main goals of surgery in the treatment of giant lesions should be:

- Maximal tumor resection reducing the mass effect of the tumor (with secondary better control of endocrine hypersecretion on functional tumors)
- Preservation or restoration of normal neurologic function
- Decompression of the pituitary gland to improve or preserve residual hormonal function.

In addition to the pituitary hormone profile, the preoperative planning for giant pituitary adenomas involves radiological investigation. The evolution of imaging studies improved the preoperative information on the pathological anatomy of the tumors, enabling surgeons to plan the intraoperative setting in greater detail. The radiological preoperative investigation for giant pituitary adenomas should always include a computed tomography (CT) angiography and magnetic resonance imaging (MRI) for bone/vessel and soft tissue assessment, respectively.

It is essential to identify the integrity of the diaphragm sellae and possible tumor extension into the subarachnoid space, suprasellar and lateral tumor extension, vessel encasement, and displacement of surrounding neurovascular structures. It may help to predict intraoperative difficulties due to pathological anatomy, and it is crucial for the approach selection.

The CT scan bone assessment provides a better idea of the surgical corridor available and allows planning of the extent of bone removal necessary for tumor resection. In addition, the CT scan also provides information on the patients' anatomy such as nasal septum deviations, integrity and degree of aeration of the paranasal sinuses (particularly the sphenoid sinus), location and presence of intersinus septae, presence of an Onodi cell, presence and extent of bone erosions, dehiscence or hyperosteosis of the skull base, and position of the internal carotid arteries.

The vascular relationships to the tumor may be evaluated through angiographic studies (CTA or Magnetic Resonance Angiogram (MRA)). The presence of arterial encasement must be assessed before surgery so the internal debulking of the tumor can proceed safely. The arterial narrowing is highly suggestive of adventitia invasion, especially in recurrent tumors previously operated and radiated.

The MRI provides information on the tumor features that are important for surgical planning:

- Tumor characteristics and signs of bleeding
- Invasion of the cavernous sinus and lateral extension
- Suprasellar extension
- Integrity of the diaphragm sellae and subarachnoid space extension
- Position of the pituitary gland
- Brain edema and pial invasion.

When the diaphragm sellae is preserved and competent, the superior limit of the tumor is usually round and smooth even in giant lesions. Lobulated tumors, irregular suprasellar contour, and brain edema are radiological signs of the tumor invading the subarachnoid space. This finding can help the surgeons to plan the approach. And when an endoscopic endonasal route is chosen it helps to anticipate whether a pedicled nasoseptal flap will be raised prior to opening the sella or if a rescue flap should be planned instead, in the hopes of reducing morbidity.

In addition, the planned endoscopic approach for a giant pituitary adenoma that seems to have a competent diaphragm sellae should be the transsellar. If there are signs of the subarachnoidal component of the tumor, an expanded endoscopic endonasal approach should be planned from the start of the procedure. Moreover, there are situations in which an expanded endonasal approach will clearly not be enough to remove the entire tumor. In these cases we recommend a combination of approaches (endonasal and craniotomy) to be performed ideally during the same anesthesia.

Tumor consistency is another important factor that influences the ability to perform an extensive resection. Even tumors with significant lateral extension or cavernous sinus invasion may be reached and resected if the tumor is soft and "suctionable". Unfortunately, there is no reliable MRI sequence that may accurately predict the tumor consistency.

Challenges in Giant Pituitary Adenoma Resection

Surgical risks are increased in giant pituitary adenomas. Giant adenomas series treated with endoscopic endonasal approach report complications rates that vary from 10% to 26.9%. The most common complications are permanent diabetes insipidus, new pituitary insufficiency, and postoperative CSF leaks. Surgery-related mortality has a low frequency in all previous studies [9].

Vascular complications risk factors are related to cavernous sinus invasion by the tumor, encasement of major intracranial vessels, and extensive destruction of the skull base, which are all known to occur with giant pituitary adenomas [10–12]. Preoperative radiological assessment and planning may anticipate such risk factors. However, postoperative acute catastrophic changes without major vessel disturbance remain extremely difficult to predict. Such acute changes are reported in 1–3% of cases of pituitary surgery; occur as vasospasm, cerebral infarction, diffuse subarachnoid hemorrhage, and postoperative pituitary apoplexy [13]; and are associated with very poor outcome regardless of early and best management.

Incomplete removal of giant pituitary adenomas may be complicated by hemorrhages of the residual tumor in the early postoperative period, resulting in acute hydrocephalus or optic nerve compression (Fig. 30.1). The probable mechanism for the postoperative pituitary apoplexy is a combination of acute ischemia, necrosis, venous congestion, edema, and raised intratumoral pressure. These mechanisms are not associated with injuries to the major intracranial vessels or perforators passing through the subarachnoid spaces, but with damage to the intratumoral feeders and/or drainers and the resultant drastic changes in the hemodynamics of the tumor.

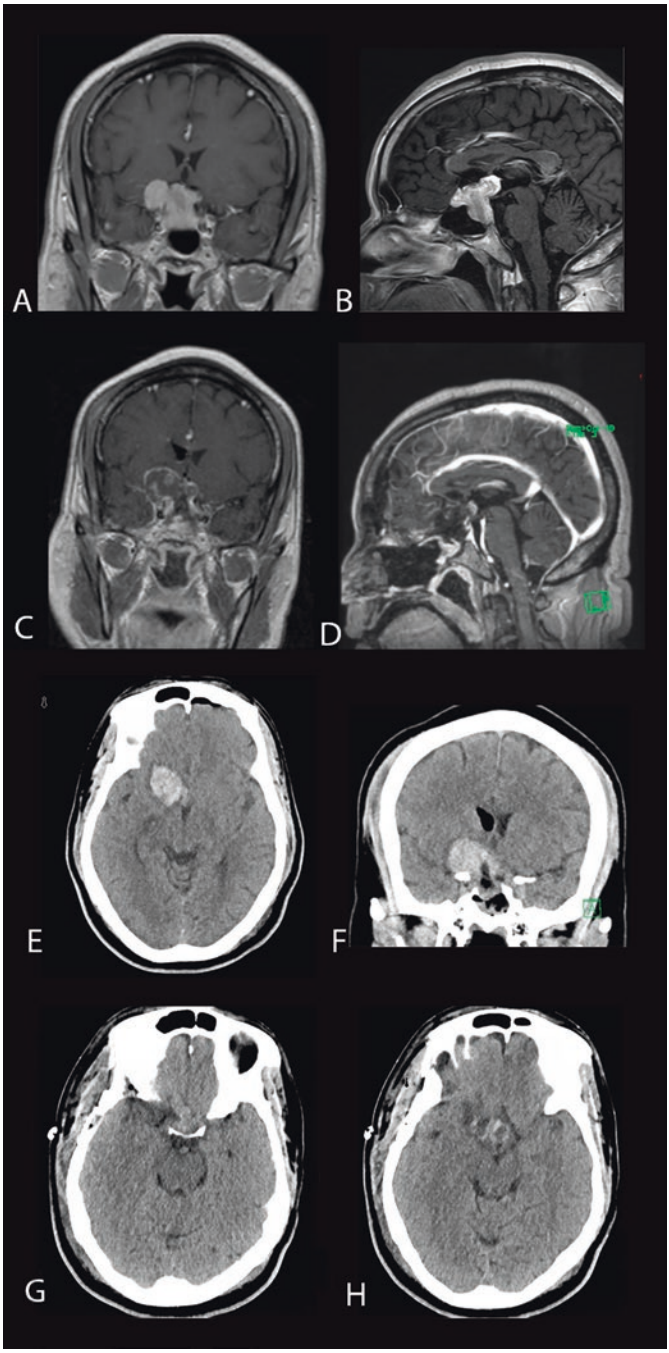

Fig. 30.1 Patient presented with bilateral visual loss. Preoperative MRI T1 W images with gadolinium showed a pituitary adenoma with suprasellar extension and subarachnoid space extravasation (**a**, **b**). The patient was operated through an endoscopic endonasal transsellar approach and experienced bilateral vision improvement. The postoperative MRI demonstrated good optic apparatus decompression (**c**, **d**). However, the patient developed acute left-side vision deterioration. Head CT scan without contrast showed postoperative pituitary apoplexy of residual tumor (**e**, **f**). The patient was taken emergently for a craniotomy and evacuation of the hematoma. Postoperative head CT scan without contrast showed complete removal of the hematoma (**g**, **h**), but the patient did not recover from his right-side visual loss

Intraoperatively, we commonly observe the darkening of tumor color and hardening in tumor consistency as we progress during the resection of these giant pituitary adenomas.

Approaching these tumors through open transcranial routes is effective for the removal of a subarachnoid, suprasellar, and lateral component of the tumor, but provides limited visualization of the intrasellar region and cavernous sinuses invasion. Furthermore, any transcranial approach puts the pituitary gland at higher risk of damage as most of the pituitary tumor is located intrasellar with the pituitary gland stretched on the periphery and particularly on top of the tumor.

On the other hand, a transsphenoidal approach provides good exposure of the midline sellar component of the tumor and allows for bilateral cavernous sinus exploration. Expanded endoscopic endonasal approaches may provide additional exposure and reach to the midline suprasellar and parasellar components of the tumor. The main limitation occurs when tumors advance in the subarachnoid space directly involving the Internal Carotid Artery (ICA), ANterior Cerebral Artery (ACA), and Middle Cerebral Artery (MCA) with respective perforators. There are also other difficult circumstances for an Endoscopic Endonasal Approach (EEA) reach where the tumor is not in the subarachnoid space, but expanded in the suprasellar through a very narrow space between the two ICAs or through the oculomotor cistern on the roof of the cavernous sinus. When facing these conditions, the surgical team must be prepared to expand the endoscopic endonasal approach or associate a combined transcranial approach in the same anesthesia or as a staged procedure (Fig. 30.2).

Management Strategy

Giant pituitary adenomas put pressure on the optic nerves and chiasm from below, which are stretched thinly over the top of the tumor. Manipulation of these nerves from above can lead to visual deterioration. Likewise, the normal pituitary gland is often stretched over the top of the tumor, and the approach from above may violate the gland to reach the tumor. Moreover, many of these tumors also invade the cavernous sinus in a medial to lateral trajectory, pushing the carotid artery and cranial nerves laterally. The tumor can be followed from below into the medial cavernous sinus, and these areas can be safely decompressed (Fig. 30.3).

Our philosophy in the management of giant pituitary adenomas is to always start with an endoscopic endonasal approach. It is the approach with the highest chance of achieving a complete tumor resection, especially with a competent diaphragm sellae. In cases where there is suspicion of subarachnoid extension of the tumor or when there is a significant lateral extension, we prepare for an open approach (supraorbital or pterional craniotomy) to be done after the EEA under the same anesthesia. An intraoperative MRI is very helpful in order to determine if a craniotomy should be performed under the same anesthesia or if the resection is satisfactory and there is low risk of postoperative apoplexy in the residual tumor. Surprisingly, in several cases for which a craniotomy was prepared this ended up not being needed because a complete tumor resection was achieved through the EEA (Fig. 30.4).

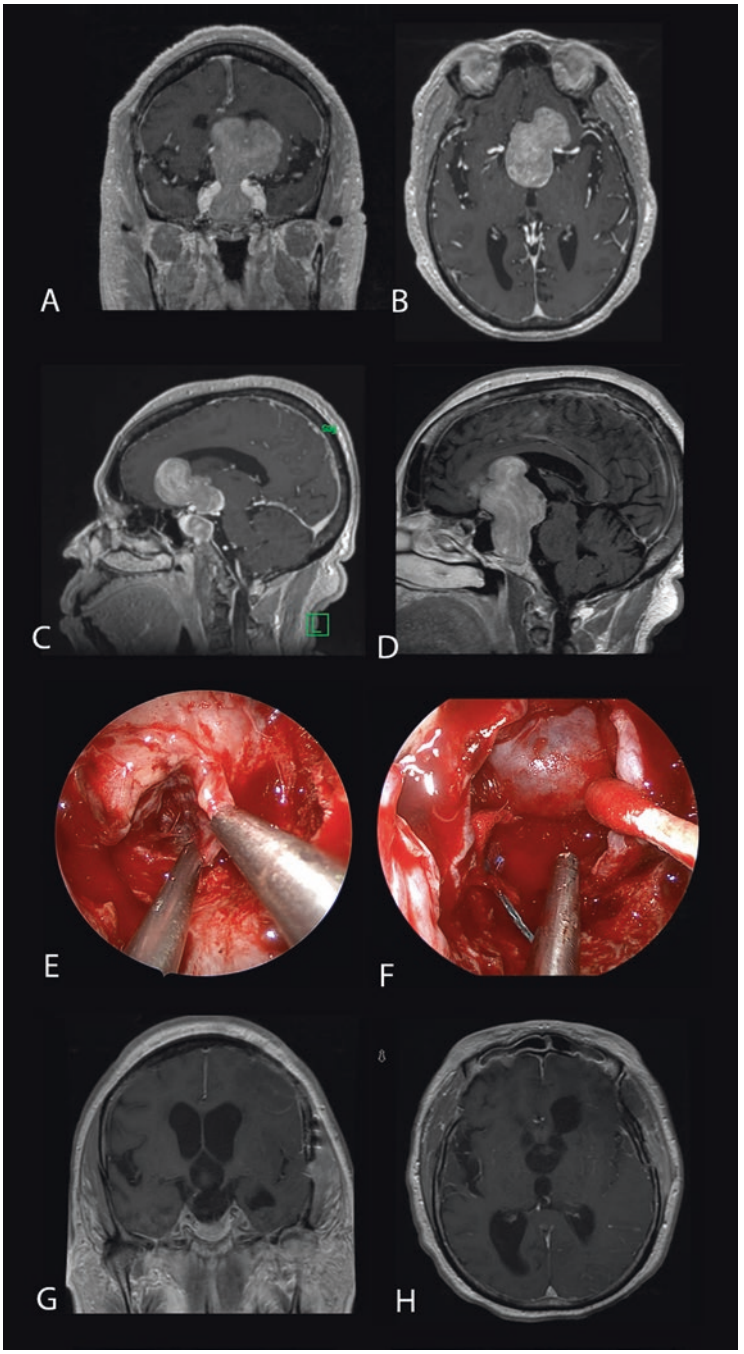

Fig. 30.2 A 65-year-old male patient presented with bilateral visual loss, functionally blind on the left side. Preoperative MRI T1 W images with gadolinium (**a**, coronal; **b**, axial; **c** and **d**, sagittal) showed a giant pituitary adenoma with suprasellar and lateral extension. A combined approach was planned with endoscopic endonasal transsellar approach (**e**, **f**) and left-side pterional craniotomy for resection of the tumor. Postoperative MRI T1 W images with gadolinium (**g**, coronal; **h**, axial) showed good resection and minimal residual tumor was intentionally left adherent to the anterior communicating artery complex

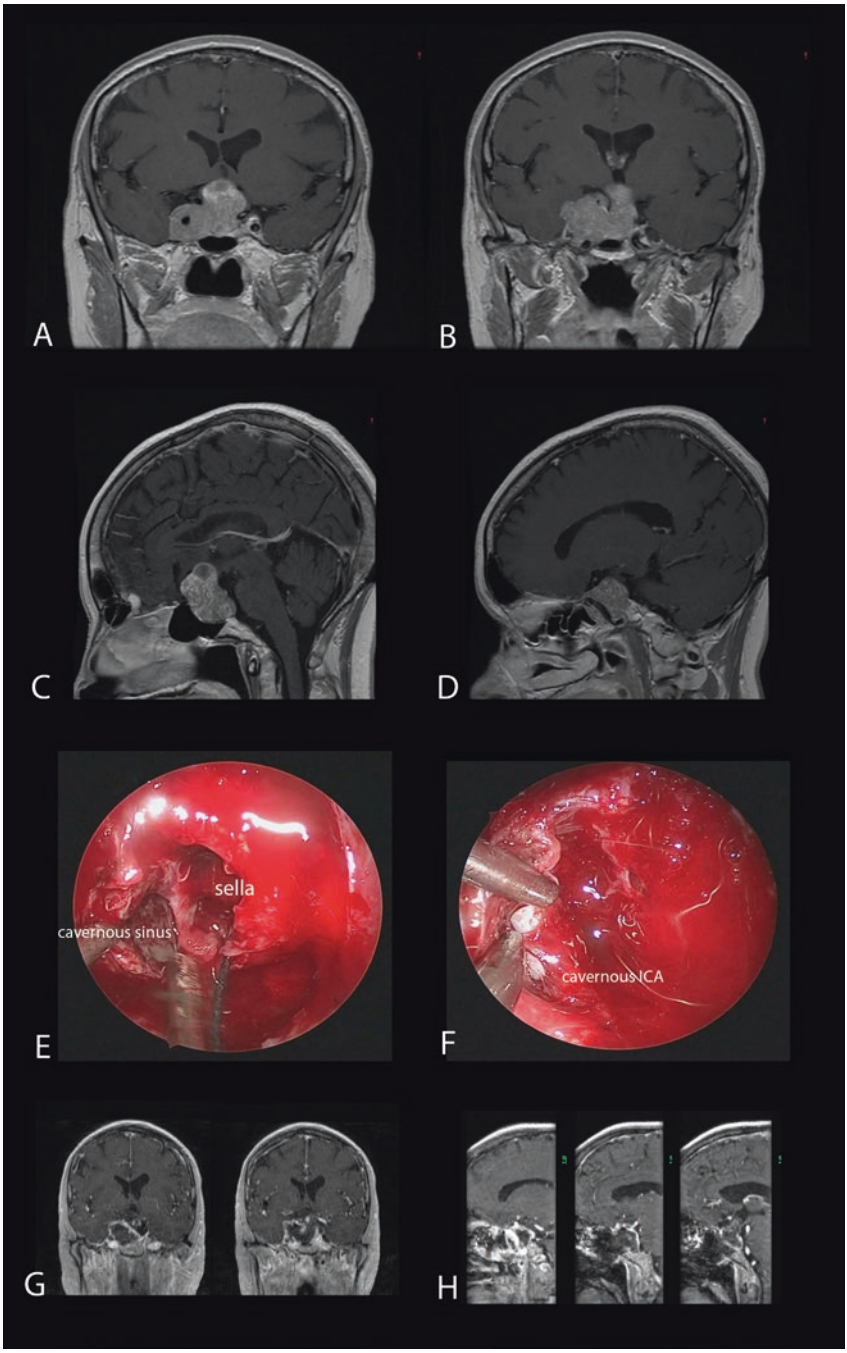

Fig. 30.3 A 50-year-old female patient with history of a previous pituitary adenoma surgery performed more than 10 years before. She was asymptomatic and experienced tumor recurrence with lateral extension and right-side cavernous sinus invasion as seen on preoperative MRI T1 W images with gadolinium (**a**, **b**, coronal; **c**, **d**, sagittal). An endoscopic endonasal transsellar approach was performed and aggressive tumor resection was achieved including the intracavernous component (**e**, **f**). Minimal residual tumor was left at the right cavernous sinus as it may be seen on postoperative MRI T1 W images with gadolinium (**g**, **h**). The patient is neurologically intact and the residual tumor has been stable for 4 years

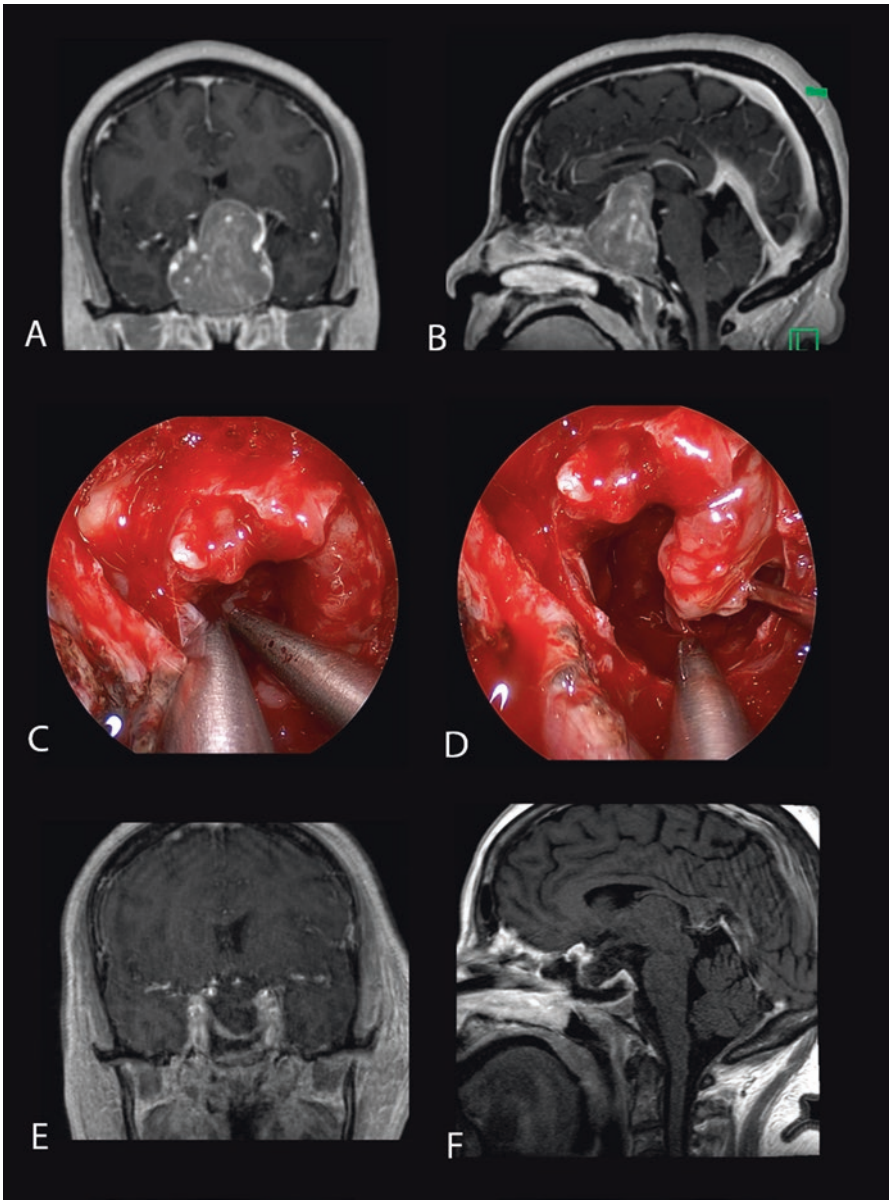

Fig. 30.4 A 42-year-old female presented with bitemporal hemianopia. Preoperative MRI T1 W images with gadolinium (**a**, coronal; **b**, sagittal) showed a giant pituitary adenoma with large suprasellar extension. We planned for a combined endonasal and trasncranial approach. An endoscopic endonasal transsellar approach was performed first (**c**, **d**) and achieved a gross total resection of the tumor. The patient developed transient diabetes insipidus in the postoperative period. Postoperative MRI T1 W images with gadolinium (**e**, coronal; **f**, sagittal) showed complete tumor resection. Follow-up after 3 years showed preserved pituitary gland function and no signs of recurrence

Surgical Approaches

Microscopic and Endoscopic Endonasal Transsphenoidal Surgery

The transsphenoidal route is the main and best surgical access to treat pituitary adenomas and involves fewer complications than transcranial procedures [1, 3, 4, 14]. Cavernous sinus invasion is one of the main limitations that precludes complete tumor resection through a microscopic transsphenoidal approach [1–3, 15, 16]. Age, type of adenoma, maximum tumor diameter, degree of suprasellar extension, retrosellar expansion, ethmoidal and nasal involvement, history of previous pituitary surgery, and type of surgery do not affect surgical outcome with the transsphenoidal approach [3]. However, dumbbell-shaped tumors or irregular adenomas and tumor extension into the subfrontal region, retrochiasmatic area, temporal region, or posterior fossa are considered contraindications for microscopic transsphenoidal surgery, and most authors suggest a transcranial approach for these cases [3, 17–19].

Several alternative surgical approaches have been described to manage these giant tumors, including the extended endoscopic transsphenoidal approach [20, 21], the staged transsphenoidal approach [22], the staged transcranial-transsphenoidal approach [23], the combined endoscopic transsphenoidal-transventricular approach [24–26], and the simultaneous combined transcranial and transsphenoidal approach [23, 27, 28].

The endoscope and the development of expanded skull base approaches have had a significant impact in neurosurgery practice in the past two decades.

Perhaps the greatest impact has been in the removal of large pituitary adenomas, where the endoscope permitted radical resection with low associated morbidity. In the past, many of these tumors were removed using a craniotomy, either alone or in combination with a transsphenoidal approach.

Considering the midline origin of the tumor and the anatomical advantages in relation to the skull base neurovascular structures, the endoscopic endonasal transsellar approach is suited for the majority of pituitary adenomas. As stated previously, even for giant adenomas, the transsellar approach should be the first surgical route in tumor management. At most experienced endoscopic endonasal centers, the need of a craniotomy to remove giant macroadenomas is extremely rare, and reserved for cases with tumor extension into the subarachnoid space that could not be removed through an EEA.

Managing giant adenomas exclusively with transcranial approaches often requires entering the cavernous sinus through the lateral wall, which places the cranial nerves in jeopardy. Operating in the lateral cavernous sinus is not only dangerous but also potentially unnecessary, particularly in nonsecreting pituitary tumors, in which residual tumor in the lateral cavernous sinus can be followed for serial growth or treated soon after surgery with stereotactic radiosurgery.

Although cavernous sinus invasion is the main limitation of open and microscopic transsphenoidal approaches, resulting in a Gross Total Resection (GTR) rate as low as 9.6% [1–3], this is not a significant limitation with EEA [29]. Invasion of the medial wall of the cavernous sinus does not restrict tumor resection with the aid

of angled endoscopes in a setting of wide exposure. This is exemplified in a publication by Koutourousiou et al. [29] showing complete evacuation of the cavernous sinus tumor in 27 (77.1%) of 35 cavernous sinuses with Knosp Grade 3 invasion and in 40 (95.2%) of 42 with Grade 0–2 invasion. The limitation of EEA was invasion of the lateral wall of the cavernous sinus and extension of the tumor to the temporal lobe. In fact, it was not the extreme lateralization of the tumor that prohibited resection, but the natural boundary of the cranial nerves at the lateral wall of the cavernous sinus [29]. In situations where the tumor enters the cavernous sinus and projects through the lateral wall in the direction of the temporal lobe, an EEA can still be considered and the tumor can be followed all the way lateral using angled scopes and angled instruments as long as the cranial nerves are monitored (Fig. 30.5). The expanded EEA may be required in cases of fibrous adenomas where the suprasellar component does not descend or the lateral component may not be resected with angled suction. To reach the midline suprasellar components of the tumor, a transtubercullum/transplanum approach is necessary (Fig. 30.6). To reach the lateral components of the tumor more specifically lateral to the cavernous ICA, a transpterygoid/transcavernous sinus approach is necessary. To reach the posterior fossa component of the tumor, a transclival approach may be required.

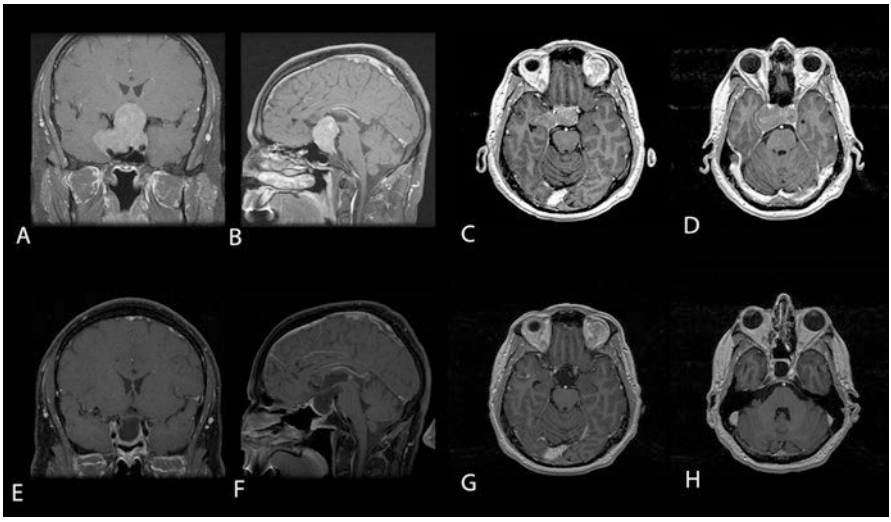

Fig. 30.5 A 55-year-old male presented with bitemporal hemianopia. Preoperative MRI T1 W images with gadolinium (**a**, coronal; **b**, sagittal; **c**, **d**, axial) showed a giant pituitary adenoma with large suprasellar extension. An endoscopic endonasal transsellar approach was performed successfully and gross total resection of the tumor was achieved with the aid of angled endoscope and instruments. Postoperative MRI T1 W images with gadolinium (**e**, coronal; **f**, sagittal; **g** and **h**, axial) showed complete tumor resection. Follow-up after 8 years showed preserved pituitary gland function and no signs of recurrence

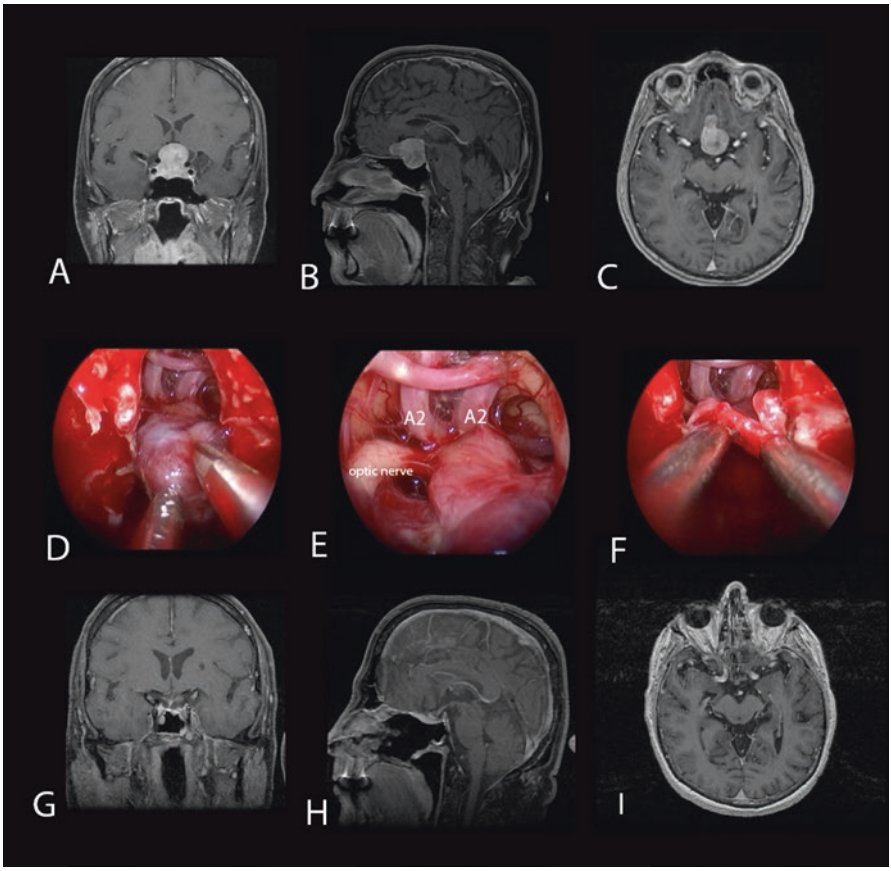

Fig. 30.6 Nonfunctioning pituitary adenoma with suprasellar extension and subarachnoid extravasation of the tumor. Preoperative MRI T1 W images with gadolinium (**a**, coronal; **b**, sagittal; **c**, axial). An expanded endoscopic endonasal transsellar/transtubercullum approach was performed with complete tumor resection (**d-f**). Postoperative MRI T1 W images with gadolinium (**g**, coronal; **h**, sagittal; **i**, axial) confirmed intraoperative impression of no residual tumor

Open Transcranial Approaches

Open transcranial approaches to ventral midline pathology of the anterior skull base are limited by a necessarily circuitous trajectory, requiring significant brain retraction in order to provide sufficient light to visualize the full extent of the tumor, particularly on tall tumors that grow in the direction of the third ventricle. They generally utilize a corridor that passes directly around cranial nerves and vascular structures, which lie between the surgeon and the tumor, in order to reach the pituitary adenoma.

These transcranial routes are usually adopted as a second choice if the transsphenoidal approach is not indicated or has failed to achieve the desired results, or when a residual adenoma cannot be reached or is in the subarachnoid region as it extravasated from the sella. When needed, our preference is for the supraorbital or pterional craniotomies depending on the required exposure.

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Postoperative Management of Patients Following Transsphenoidal Surgery

31

Martin J. Rutkowski and Sandeep Kunwar

Introduction

Endonasal transsphenoidal surgery offers access to the anterior, middle, and posterior cranial fossa and is particularly efficacious for sellar lesions, even those with suprasellar extension, cavernous sinus invasion, and sellar and clival infiltration. With the widespread adoption of these techniques, largely obviating the need for sublabial and transcranial approaches, postoperative care is becoming increasingly standardized and simplified [13, 14].

The high prevalence of pituitary adenoma [15]—estimated at 15%—renders this the most commonly treated pathology. Other accessible lesions include craniopharyngioma, tuberculum and planum sphenoidale meningiomas, dermoids, epidermoids, and miscellaneous infundibular and hypothalamic lesions including germinomas, granulomas, and hamartomas. Whether accessed with the operating microscope or the endoscope, excellent rates of gross total resection can be achieved with minimal associated morbidity.

The nature of a patient's pathology largely determines the course of their postoperative care, as does the adjacent neurovascular anatomy and sinonasal anatomy accessed during endonasal, transsphenoidal approaches. In this context, the practitioner should be aware of the following management considerations in both the immediate postoperative inpatient setting and during outpatient follow-up. The protocols used in our center are influenced by the discharge of the majority of our patients on the first postoperative day.

M.J. Rutkowski, MD
Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA, USA

S. Kunwar, MD (✉)
California Center for Pituitary Disorders, Department of Neurological Surgery, University of California, San Francisco, CA, USA
e-mail: Martin.Rutkowski@ucsf.edu

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_31

Inpatient Considerations

Postoperative Steroids

We advocate perioperative and immediate postoperative steroid administration for any sellar or parasellar pathology given the consequences of postoperative hypocortisolism from pituitary manipulation or stunning. While the incidence remains low, administration of steroids perioperatively can prevent potentially severe complications of postoperative hypocortisolism including hemodynamic instability, weakness, altered mental status, and hypoglycemia.

In the unique case of Cushing's disease, we recommend no administration of steroids or the use of 1 mg of dexamethasone perioperatively; this low dose adequately provides steroid coverage in the immediate postoperative window, is low enough to avoid cortisol suppression and a false positive cure on postoperative cortisol follow-up, and will not interfere with postoperative cortisol testing given that the drug is synthetic and does not show up in routine testing of cortisol on postoperative day 1.

We typically continue low-dose steroid replacement therapy using 0.25 mg of dexamethasone daily until 2 days prior to follow-up at which time an AM cortisol is performed and replacement therapy is resumed until adequate endogenous cortisol levels are confirmed. In the setting of low normal levels of cortisol, in patients with larger tumors, and in patients with preoperative hypocortisolemia, a CRH-stimulation test is also performed. If patients remain in the hospital for longer periods of time, reassessment of cortisol production can be done sooner. For patients with Cushing's disease, if the immediate postoperative cortisol level is subnormal or normal, replacement therapy is initiated at the same dose or with twice-a-day scheduling. These patients will require replacement therapy until the normal CRH/ACTH axis reawakens.

Postoperative Hormone Testing

In cases of functional pituitary adenoma, hormone screening on the morning of postoperative day 1 can provide an early indication of biochemical remission. In Cushing's disease, a postoperative cortisol <2 μg/dL is associated with cure in Cushing's disease, whereas normal values can suggest residual disease with recurrence rates of 24% [17]. However, subnormal cortisol levels do not always correlate with cure, and normal levels do not always correlate with residual disease. Moreover, there is certainly a need for close monitoring following initial resection [12, 17]. Serum levels of growth hormone and prolactin should similarly be checked on the morning of postoperative day 1. Growth hormone levels <1.0 μg/L (with or without an oral glucose tolerance test) have been associated with long-term remission [21]. IGF-1 has a prolonged half-life and therefore should be measured 6–12 weeks after resection. Some practitioners routinely check a morning cortisol on all patients undergoing endonasal transsphenoidal surgery in the sellar/parasellar region [9, 16], though this practice is variable.

Sodium and Water Homeostasis

Given the close proximity of the pituitary infundibulum and hypothalamus to the sella, postoperative care of patients undergoing endonasal transsphenoidal approaches necessitates close monitoring of sodium given the possibility of diabetes insipidus (DI) and syndrome of anti-diuretic hormone (SIADH) following surgery. Indeed, delayed hyponatremia has been shown in multiple series to be one of the most common causes of readmission following transsphenoidal surgery [1, 7]. Thus, obtaining a morning serum sodium on postoperative day 1 provides an important early indicator of a patient's salt and water balance.

Disorders of salt and water balance can be seen postoperatively, even in cases of microadenoma. When present, DI is thought to be secondary to transient "stunning" of the infundibulum from manipulation or minor stretch injury, and vasopressin stores are unable to be released from the neurohypophysis. This results in a usually transient DI, with dilute urine in the setting of hypernatremia and polydipsia. This can be diagnosed with a morning serum sodium check on postoperative day 1; however, in patients with high urine output and low urine specific gravity, serum osmolality and urine studies including sodium and osmolality can be useful. Treatment is largely supportive; most patients with an intact thirst mechanism are able to maintain eunatremia with access to free water. When present, transient DI can be followed with daily sodium and strict monitoring of patients' fluid intake and output. In select cases of refractory DI, vasopressin can be administered until sodium normalizes. Patients can be sent home with vasopressin as needed for high urine output with strict instruction to correlate their fluid intake with thirst.

SIADH is more often encountered postoperatively and is generally diagnosed by a low sodium (Na < 135) postoperatively. As its name implies, manipulation of the hypothalamus or infundibulum can cause excess release of vasopressin stores, leading to euvolemic hyponatremia caused by excess renal water resorption. In a series of 1013 consecutive operations, 16% of our patients were found to have hyponatremia, with 19% having symptoms of hyponatremia including headache, dizziness, nausea, and vomiting. Two percent required readmission for fluid management and frequent sodium monitoring [18]. The typical timing for symptomatic hyponatremia is shown in Fig. 31.1 and mean time for patient readmission is 4–8 after surgery [18–20]. Mild hyponatremia (Na > 130) can be managed as an outpatient with fluid restriction, sodium supplementation, and daily serum Na checks until normalization. For patients with more significant symptoms or Na < 130, admission with more frequent serum Na checks, fluid restriction, and sodium supplementation through 3% NaCl infusions in more severe cases (Na < 125) are the main steps in treatment. Finally, the vaptan family of drugs, competitive inhibitors of the V2 receptor within the kidney, can be helpful for refractory cases of SIADH or where more rapid correction is needed [2, 10].

The risk for symptomatic hyponatremia has been associated with preoperative hypopituitarism, lower BMI, and trended with increased age [18–20]. Female patients were also at higher risk [20]. Although postoperative hyponatremia is often a transient self-correcting phenomenon, strategies for prompt identification of

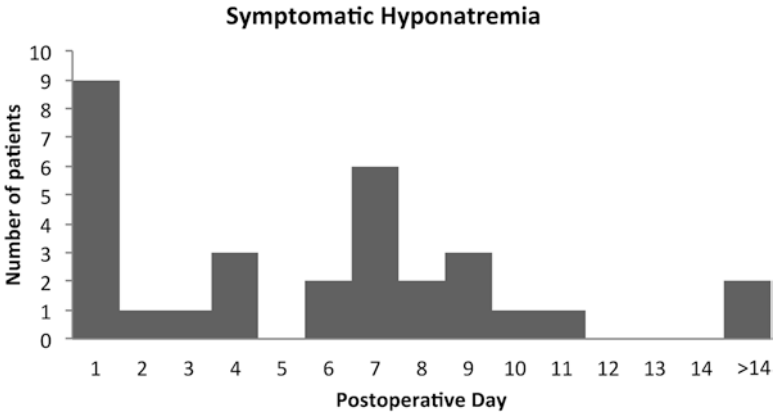

Fig. 31.1 Delayed symptomatic hyponatremia peaked on postoperative day 7 and rarely occurred after day 12

hyponatremia in high-risk patients should be in place with screening of serum Na in the first 2 weeks after surgery for any patient presenting with increased symptoms of headaches, nausea, or vomiting.

Imaging

Given the largely benign nature of lesions in the sellar/parasellar region, immediate postoperative imaging is frequently unnecessary. Furthermore, magnetic resonance imaging (MRI) beyond 48 h postoperatively can be difficult to interpret given the similar appearance of scar tissue and possibly residual tumor. Therefore, we do not routinely perform postoperative imaging studies in the inpatient setting and advocate obtaining scans at least 6–12 weeks postoperatively to allow tissues to heal and postoperative changes to resolve. At this time, the presence or absence of residual tumor can be discussed with patients, including further management options such as repeat surgery, radiation-based adjuvant therapies, and/or medical therapy. Indications for immediate postoperative imaging include changes in neurological exam including confusion or vision changes.

Outpatient Considerations

Sinonasal Corridor

The national movement toward adoption of the endoscope [11] has resulted in greater use of otolaryngologists as cosurgeons, due both to their expertise in navigating the sinonasal corridor and to the occasional use of expanded approaches that can involve resection of the turbinates, passage through the ethmoid and maxillary

sinuses, and reconstruction techniques such as use of nasoseptal flaps. While otolaryngologists may assist in the perioperative and postoperative management of sinonasal morbidity, most postoperative sinonasal care can be administered effectively by neurosurgeons.

Nasal packing and prophylactic antibiotics can be utilized, though in our practice both are rarely necessary for traditional endonasal approaches to the sella. While sinusitis can occur several weeks postoperatively, patients should be counseled that nasal stuffiness and discharge commonly persist several weeks postoperatively, and unless there is concern for frank cerebrospinal fluid (CSF) leakage or gross purulence, these symptoms largely resolve within 1 month. When correlated with persistent clinical symptoms indicative of bacterial infection, sinusitis that is seen on postoperative imaging can be treated with a course of antibiotics.

Epistaxis may also be encountered postoperatively, though most surgical series demonstrate rates <5% [3, 7]. The transition to the endonasal approach compared to sublabial is correlated to a slight increase in postoperative epistaxis. Severe cases are most often secondary to hemorrhage from the sphenopalatine artery [3], in which consultation with an otolaryngologist may prove helpful. Deep packing can be done in the outpatient setting, while return to the operating room or angiography suite for more definitive embolization of the internal maxillary artery is rarely necessary.

Lost or diminished olfaction can prove a vexing issue for patients postoperatively. Watchful waiting is often necessary, as resumption of olfaction can occur in a delayed fashion. The best strategy is a prophylactic one, in which the septal olfactory mucosa, located within the superior portion of the septal mucosa, is spared during endonasal approaches by leaving the uppermost 1–2 cm of septal mucosa intact [6]. Even when necessary, nasoseptal flaps that spare this region can remain well vascularized and be of adequate size to seal off most intraoperative CSF leaks and/or reconstruct the anterior sella [6].

Visual Field Testing

When lesions abut, displace, or encase the optic nerves, chiasm, or distal pathways, patients often present with visual dysfunction in the form of field cuts, diplopia, and blurred vision. Formal preoperative testing with an ophthalmologist aids the neurosurgeon in preoperative counseling and operative planning, as goals for resection can change dramatically based on pathology and proximity to the optic apparatus. In patients with any preoperative visual deficits or concern for new deficits following endonasal transsphenoidal approaches, postoperative visual field testing can prove invaluable for the formal documentation of baseline postoperative function. Typically, repeat visual fields are performed 3 months after surgery. Patients can then be followed with routine testing to assess for improvement, which can often take up to 1 year to manifest [4, 5, 8].

Biochemical Follow-Up

While evidence of cure for nonfunctional adenoma is provided radiographically, postoperative care for patients harboring functional pituitary adenomas should include routine hormone screening 1–3 months postoperatively to ensure biochemical remission. Depending on the hormone subtype, i.e., corticotrophs, somatotrophs, lactotrophs, or mixed variants, follow-up with a neuroendocrinologist can be essential to ensure that hormone levels are appropriately normal or subnormal following adenoma resection. Furthermore, hormone replacement therapy is often necessary in the form of sex hormone replacement, thyroid replacement, and steroid replacement, all or none of which may be gradually weaned off, if and when native pituitary function returns.

Long-term follow-up for disease recurrence can also be performed under the care of a neuroendocrinologist by performing regularly scheduled hormone testing. When combined with serial imaging, these data can prove invaluable for long-term disease monitoring and early detection of tumor recurrence.

Nonpituitary suprasellar pathology, such as craniopharyngioma, Langerhans histiocytosis, or germinoma, may first present with diabetes insipidus and thus require postoperative monitoring of salt and water balance. Postoperative administration and utilization of vasopressin is best handled in conjunction with a neuroendocrinologist.

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Stereotactic Radiosurgery for Pituitary Adenomas

32

Cheng-Chia Lee and Jason P. Sheehan

Key Points

- Stereotactic radiosurgery is indicated for residual or recurrent functioning and nonfunctioning pituitary adenomas. It offers a high rate of tumor control and hormone remission.
- A higher margin dose is required to achieve endocrine remission in functioning adenomas. The rate of endocrine remission after radiosurgery appears faster than that achieved with fractionated radiation therapy. A low rate of serious complication can be found in patients who underwent radiosurgery.
- The most frequent complication following radiosurgery of a pituitary adenoma is hypopituitarism. However, panhypopituitarism occurs only rarely.

Introduction

Pituitary adenomas are quite common among the general population and comprise 10–20% of all intracranial tumors [67]. They are classified by hormonal secretory status, with hormone hypersecretion from functioning lesions and absence of abnormal hormonal production comprising nonfunctioning lesions, and by size with microadenomas less than 1 cm in diameter and macroadenomas at least 1 cm in diameter. While their macroscopic appearance and anatomical location are relatively homogeneous, pituitary tumors have the potential to generate a wide variety

C.-C. Lee
Department of Neurosurgery, University of Virginia, Charlottesville, VA, USA

J.P. Sheehan (✉)
Department of Neurological Surgery, University of Virginia, Charlottesville, VA, USA

Department of Radiation Oncology, University of Virginia, Charlottesville, VA, USA
e-mail: jsheehan@virginia.edu

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_32

of clinical sequelae. Nonfunctioning pituitary adenomas enlarge progressively in the pituitary fossa and often extend beyond the sella turcica. The enlargement of the tumor may cause mass effects, including visual field deficits resulting from optic apparatus compression and hypopituitarism resulting from compression of the normal pituitary gland. For functioning pituitary adenomas, prolactinomas result in amenorrhea-galactorrhea syndrome, growth hormone (GH)-secreting adenomas cause acromegaly in adult and gigantism in child, adrenocorticotropic hormone (ACTH)-secreting adenomas cause Cushing's disease.

Treatment options for pituitary tumors include medical therapy, microscopic or endoscopic transsphenoidal surgery, radiosurgery, radiation therapy, or observation depending on the biochemical profile and clinical status of the patient. Stereotactic radiosurgery (SRS) is usually indicated for incomplete surgical resection leaving residual tumor, tumor recurrence, or failure of medical therapy. In this chapter, the principle and method of the SRS for pituitary tumors are discussed. We especially focused on the nonfunctioning adenoma, GH-secreting adenomas, and ACTH-secreting adenomas. While post-radiosurgery radiographic tumor control for nonfunctioning/functioning adenomas is excellent, typically around 90%, the rates of endocrine remission for functioning adenomas are lower than the tumor control rates. The highest endocrine remission rates are achieved in patients with Cushing's disease and the lowest in those with prolactinomas. Endocrine remission rates vary from 30 to 80%. Because of the rare but well-documented occurrence of late recurrence following endocrine remission, long-term and rigorous clinical and radiographic follow-up is necessary for all pituitary adenoma patients treated with SRS.

History

The Gamma Knife radiosurgery (GKRS), one of the most popular modalities of SRS, was first employed by Leksell to treat the pituitary adenoma patient in 1968. Initially conceived by Lars Leksell in 1951, GKRS delivers a single high, concentrated dose of radiation to the target. According to Leksell's series in 1980, 95 patients with Cushing's disease and Nelson's syndrome have been treated by gamma radiation [33, 55]. Small and spatially well-defined volumes of tissue in the pituitary gland can be selectively destroyed. With the smallest collimator, a kind of intracellular "micro-radiosurgery" is possible. In a review of 37 patients with an observation time of more than 1 year, complete remission was obtained in 29 cases. This was a promising result. Since then, radiosurgical devices and techniques have been significantly refined and thousands of pituitary adenoma patients have been treated in the interim.

Around the time of Leksell's development of the Gamma Knife), innovative work in the field of radiosurgery using heavy particles from cyclotrons was conducted by Raymond Kjellberg and Jacob Fabrikant. Later, in 1983, at a hospital in Buenos Aires, Betti and Derechinsky developed the concept of a modified linear accelerator for SRS [2, 3]. Their system relied upon a 10 MV linear accelerator, and

it utilized a chair for the patient which was based upon the Talairach stereotactic frame [44]. Other innovative developments in linear accelerator-based SRS devices followed shortly thereafter from Winston and Lutz in Boston, Hartman and Sturm in Heidelberg, Barcia-Salorio in Valencia, Colombo in Vincenza, and Podgorsak in Canada [2, 3, 11, 16, 43, 51].

Treatment Strategy and Patient Selection

Based on the clinical features of different types of pituitary adenomas, and biochemical assessment according to recommended endocrine guidelines, initial diagnosis of pituitary adenomas can be made in the most of time. For the patient with a pituitary adenoma except prolactinoma, a surgical resection via transsphenoidal surgery or craniotomy is recommended. For the patient with a prolactinoma, the medications including bromocriptine and cabergoline are suggested, and the surgical resection is only for the dopamine agonist-resistant prolactinomas (Fig. 32.1).

SRS is typically indicated for residual or recurrent functioning and nonfunctioning pituitary adenomas. If a patient has a neurological deficit attributable to an adenoma, surgical resection is the initial treatment of choice for all tumors except a prolactinoma. Transsphenoidal surgery (endoscopic or microscopic) allows for the most rapid relief of mass effect and reduction in excessive hormone levels in patients with Cushing's disease and acromegaly. Prior surgical resection also facilitates subsequent radiosurgery, and a clinician can always prescribe higher dose with safe margin, which is especially important for hormone remission of functioning adenomas.

Treatment strategy for a pituitary adenoma

	Nonfunctioning adenoma	Cushing disease	Acromegaly	Prolactinoma
1st line	Surgical resection	Surgical resection	Surgical resection	Medication: dopamine agonists
2nd line	Radiosurgery	Radiosurgery	Radiosurgery	Surgical resection
3rd line		Medication: ketoconazone and metopirone	Medication: Octreotide	Radiosurgery
4th line		Adrenalectomy	Medication: GH receptor antagonist and dopamine agonist	

Fig. 32.1 Treatment strategies for a pituitary adenoma

Pre-SRS Evaluation

All patients suspected of harboring a pituitary tumor should undergo a complete endocrine evaluation, neuro-imaging study, and ophthalmic examination before SRS. Endocrine studies should be done through each facet of the hypothalamic-pituitary-end organ axis, including growth hormone (GH), insulin-like growth factor-1 (IGF-1), adrenocorticotropic hormone (ACTH), serum cortisol, prolactin, T4 or free T4, thyroxin-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone (men) levels. Imaging studies consisted of magnetic resonance imaging (MRI), with and without contrast using thin slices, and volume acquisition through the region of the sella turcica. The ophthalmological evaluation typically includes visual acuity and visual field testing.

Radiosurgical Technique and Planning

Radiosurgery is characterized by a steep dose fall-off, thereby relatively sparing radiation exposure to surrounding normal tissues. The use of a single high dose of ionizing beams to treat intracranial disorders was a creative concept in the 1960s. Nowadays, radiosurgery has been a multidisciplinary discipline. The definition sanctioned by the AANS, CNS, and ASTRO call for delivery of radiosurgery by a team consisting of a neurosurgeon, radiation oncologist, and medical physicist [1]. Similarly, the American College of Radiology recommended a similar multidisciplinary approach to insure quality of care and went so far as to specify specific responsibilities during the SRS process for the individual members of the multidisciplinary team [57].

Stereotactic Frame Replacement

Patients underwent stereotactic frame placement (e.g., Leksell frame for Gamma Knife, Elekta Instruments, Inc.), and supplemented by local anesthesia and conscious sedation as needed [68]. Prior to frame placement, the scalp is disinfected with alcohol, and the areas of the pin placements are infiltrated with long-acting local anesthetics. The use the angle of the optic apparatus as the axis of frame is usually helpful. This angle approximates a line joining the lateral canthus and the top of the pinna, and it makes identification of the optic nerves, chasm, and tracts easier by having an image that demonstrates the entire optic apparatus in a single MRI slice [17].

For patients treated with LINAC-based systems (e.g., Edge by Varian or Cyberknife by Accuray) and the newer Gamma Knife Extend or Icon, different immobilization systems besides a rigid stereotactic frame are used. These may include a relocatable frame or a thermoplastic mask. Onboard imaging including cone-beam CT or infrared tracking can be used to compensate for a reduction in immobilization with less rigid devices.

Radiographic Images

Preplanning with images can be obtained in advance of immobilization. Such studies should be tomographic in nature and can be co-registered to later obtained stereotactic neuro-imaging datasets.

After stereotactic frame replacement, all patients underwent thin-sliced stereotactic MRI with and without intravenous contrast administration. Imaging studies were also obtained for all patients using standard pituitary magnetic resonance (MR) imaging sequences. At the University of Virginia, pre-contrast sequences included coronal and sagittal T1-weighted (1 mm sections), fast spin echo (FSE) axial and coronal T2-weighted (1 mm sections) images. The post-contrast sequences included coronal T1-weighted (1 mm sections), sagittal FSE T1-weighted (1 mm sections), and coronal spoiled gradient echo (SPGR) T1-weighted images. Fat suppression MRI techniques are of particular value to patients with prior resections and associated grafts placed in or around the sellar/parasellar region. Since 2010, dynamic MR imaging sequences were utilized as part of radiosurgical planning sequencing [48, 49, 52].

For patients who cannot tolerate an MRI, CT may be an alternative option. Nevertheless, the accuracy is usually less and the lesions are blurred, especially when patient had undergone prior surgical resection. Positron emission tomography (PET) imaging may also be of value for detecting hypersecretory adenomas; such images can be overlaid on stereotactic tomographic images (e.g., MRI or CT), but such PET scans are typically co-registered to a stereotactic MRI and/or CT [34].

Regardless of the radiosurgical modality used, stereotactic radiosurgery requires clear and accurate imaging of that target. Advances in radiographic imaging over the past 20 years have increased the efficacy and safety of radiosurgical treatment of pituitary lesions.

Treatment Planning and Dose Selection

The current treatment planning for a pituitary adenoma is usually performed in the computer-based software (e.g., Gamma Plan, Elekta Instruments, Inc.). First of all, the target lesion and the surrounding structures are contoured. Second, a dose plan can be rendered to deliver an ideal dose to the target and a safe dose to adjacent critical structures. Third, conformality, dose uniformity, and gradient index should be assessed and adjusted so as to optimize the dose plan.

In general, single session radiosurgical margin doses vary from 12 to18 Gy for nonfunctioning adenomas and from 15 to 30 Gy for functioning adenomas [20, 21, 58, 60–62]. Because the systemic effects of functioning adenomas can be so devastating, it seems intuitive to deliver a reasonably high dose (> = 20 Gy to the margin) to allow rapid hormonal normalization and control of tumor growth. For improved rates of hormonal normalization in functioning adenomas, margin dose of 25 or 30 Gy may even be chosen. However, it is not known to what degree a higher margin dose (e.g., 20 vs 30 Gy) will result in delayed hypopituitarism. In cases of functioning adenomas with radiologically identifiable targets in the cavernous sinus,

radiosurgical plans can be devised with higher range treatment doses while shielding much of the normal stalk, gland, and optic apparatus. Nonfunctioning pituitary adenomas appear to require a lower radiosurgery treatment dose than functioning adenomas [35, 62]. The lowest effective dose for a nonfunctioning tumor is not unknown, but many centers deliver 12–15 Gy to the margin.

Care should be taken to avoid high doses or "hot spots" to critical neurovascular structures, such as the optic apparatus around the tumor, cranial nerves or carotid artery within the cavernous sinus region. Radiosurgery can be hypofractionated in 2–5 sessions to deliver a more optimal dose plan tailored to the constraints of a particular case. In cases of hypofractionated SRS, the optimal margin dose and constraints to critical structures vary with the target volume, proximity to adjacent structures, history of prior radiation, and dose-fractionation scheme selected. Careful consideration of the normalized BED to the adenoma and critical structures should be given in hypofractionated SRS approaches.

From previous literature, visual deterioration following SRS is rare and can be avoided if the dose to the optic apparatus is restricted to ≦8 Gy, although some groups reported that the optic apparatus was exposed to 10–12 Gy without complications [28]. Transitionally, a distance of 3 mm or more between the rostral extent of the adenoma and the optic apparatus is desirable. Although the absolute distance between the optic apparatus is not the limiting factor, rather it defines how steeply the radiation gradient must be constructed so that a tolerable dose is delivered to the optic apparatus while still delivering an effective dose to the adenoma. If an acceptable gradient cannot be constructed, then alternative treatment should be considered. Modern radiosurgical devices may allow a distance of as little as 1–2 mm [36, 59, 70]. Ultimately, the tolerable absolute dose permitted likely varies from patient to patient, and it is affected by factors such as previous damage to the optic apparatus by pituitary adenoma compression, ischemic changes, type and timing of previous interventions (e.g., fractionated radiation therapy and surgery), the patient's age, and the presence or absence of other comorbidities.(e.g., diabetes or hypertension) [21, 54].

Compared to the optic apparatus, the majority of cranial nerves in the cavernous sinus appear to be more resistant to radiation effects, but reports of cranial neuropathy, particularly after repeat radiosurgery, are well documented [21]. Although the tolerable limit to the cavernous sinus nerve is unknown, reports have detailed effective radiosurgical doses of between 19 and 30 Gy to this region with a low risk of appreciable side effects [25, 38, 46, 50, 59]. Injury to the cavernous segment of the carotid artery is rare after SRS, with only one isolated case report [35].

Outcomes of Radiosurgery for Nonfunctioning Pituitary Adenomas

Because the endocrine presentation is silent, the primary radiosurgical goal for nonfunctioning adenomas is radiologic tumor control. SRS resulted in tumor control rates of 94–97% at 5 years and 76–87% at 10 years of follow-up, and new-onset hypopituitarism following radiosurgery was observed in 2–30% with a median of 21% [19, 37, 48, 62, 65]. Table 32.1 lists the major radiosurgical series for nonfunctioning adenoma

Table 32.1 The largest five radiosurgery series for nonfunctioning pituitary adenomas

Study	Year	*n*	FU period (mo)	Margin dose (Gy)	Tumor control (%)	Hypopituitarism (%)	New onset CN deficits (%)
Liscak et al. [37]	2007	140	60	20	100% at 5 years	2	0%
Iwata et al.[a] [19]	2011	100	33	21Gy/3Fr, 25Gy/5Fr	98% at 3 years	4	1%
Park et al. [48]	2011	125	62	13	99, 94, and 76% at 1, 5, and 10 years	24	0.8% from CN2, 1.6% from other CN
Starke et al. [65]	2012	140	50	18	98, 97, 91, and 87% at 2, 5, 8, and 10 years	30.3	12.8% from CN2, 0.9% from other CN
Sheehan et al.[b] [62].	2013	512	36	16	98, 95, 91, and 85% at 3, 5, 8, and 10 years	21	6.6% from CN2, 2.7% from other CN

Abbreviation: *CN* cranial nerve, *Fr* fraction, *FU* follow-up, *Gy* gray, *mo* month, *NA* not available
[a]Cyberknife series, others were Gamma Knife
[b]From a multicenter study

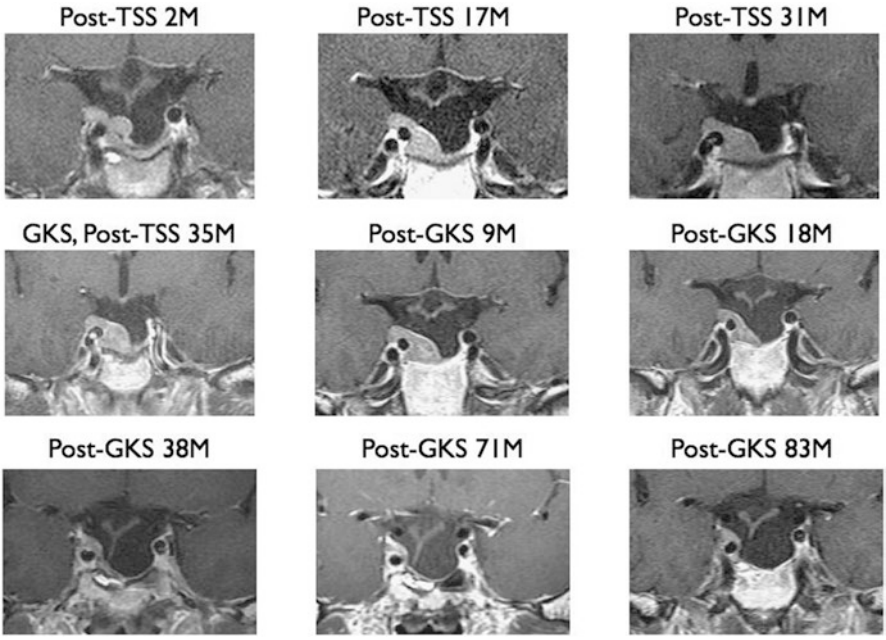

Fig. 32.2 A 38-year-old female patient with a nonfunctioning adenoma underwent two transsphenoidal surgeries in 1997 and 2004. There was a small residual tumor on right sellar floor and right cavernous sinus, and the residual tumor was slowly growing within 3-year follow-up. After radiosurgery, the tumor was progressively regressed and almost gone in the last follow-up 83 months after radiosurgery. No visual deterioration and hormone deficiency was found during 7-year follow-up (*TSS* transsphenoidal surgery, *GKS* Gamma Knife radiosurgery, *M* month)

patients until 2015. In a recent multicenter trial evaluating the role of SRS for 512 patients with nonfunctioning pituitary adenomas (median follow-up of 36 months; range 1–223 months), an overall tumor control rate of 93% was reported [62]. Favorable outcomes of tumor control and neurological preservation were more commonly seen in patients older than 50 years, those with a tumor volume less than 5 cc, and those without prior fractionated radiation therapy or prior radiosurgery [62]. The illustrative case with a nonfunctioning pituitary adenoma is showed in Fig. 32.2.

Outcomes of Radiosurgery for Functioning Pituitary Adenomas

Unlike nonfunctioning adenomas, the primary radiosurgical goals for functioning adenomas are both endocrine remission and radiologic tumor control. Radiological tumor control usually accompanies endocrine remission, but some adenomas exhibit tumor control yet fail to achieve endocrine remission. Radiosurgery plays an important role in the treatment of persistent Cushing's disease, acromegaly, and some prolactinomas refractory to surgical and/or medical management.

For Cushing's disease, endocrine remission is typically defined as a normal 24-h urinary free cortisol (UFC) and serum cortisol. Most radiosurgical series for Cushing's disease demonstrate endocrine remission in the majority of patients after radiosurgery; the remission rate across major series is 28–70%. The mean time interval after radiosurgery to endocrine remission in successfully treated cases is 12 months [8, 12, 21, 24, 63, 69]. Table 32.2 details recent major radiosurgical series for Cushing's disease. Higher radiosurgical doses typically required to attain endocrine remission in Cushing's disease compared to those used to control the growth of nonfunctioning adenomas. Delayed endocrine recurrence after radiosurgery-induced remission may occur. For instance, in a radiosurgical series of 90 Cushing's disease patients with a mean follow-up of 45 months, recurrence of Cushing's disease occurred in 10 patients at a mean time of 27 months after initial remission [21]. The illustrative case with Cushing's disease is showed in Fig. 32.3.

For acromegaly, endocrine remission varied (range 0–82%) across series because of the different remission criteria. In general, endocrine remission for acromegaly was typically defined as a normalization of IGF-1 or nadir serum GH < 2.5 μg/dL [32]. By meeting the criteria, the remission rate for acromegalic patients after radiosurgery was 53–60% at 5-year follow-up [9, 14, 23, 32, 41, 69]. Some of the radiosurgical series use the results of oral glucose tolerance test (OGTT) to define endocrine remission for acromegaly (Table 32.3). From prognostic factor analysis, patients with a functioning adenoma volume of less than 3 cc at the time of radiosurgery have been noted to have significantly higher chance of endocrine remission following radiosurgery [61]. Thus, maximum safe surgical resection prior to radiosurgery increases the chance of endocrine remission. At the University of Virginia, the median time to endocrine remission after radiosurgery for acromegaly was 24 months, and this was longer than for comparable Cushing's disease patients [61]. Although drawn from retrospective studies, there appears to be compelling evidence to temporarily halt pituitary suppressive medications around the time of

Table 32.2 The largest five radiosurgical series for Cushing's disease

Study	Year	*n*	FU period (mo)	Margin dose (Gy)	Endocrine remission (%)	Hypopituitarism (%)	New onset CN deficits (%)
Devin et al.[a] [12]	2004	35	42	15	49	40%	0%
Castinetti et al. [8]	2007	40	55	30	43	15%	5%
Kobayashi et al. [24]	2009	30	64	29	35	N/A	N/A
Wan et al. [69]	2009	68	67	23	28	N/A	N/A
Sheehan et al. [63]	2013	96	48	22	70	36%	5.2%

Abbreviation: *CN* cranial nerve, *Fr* fraction, *FU* follow-up, *Gy* gray, *mo* month, *NA* not available
[a]From LINAC series

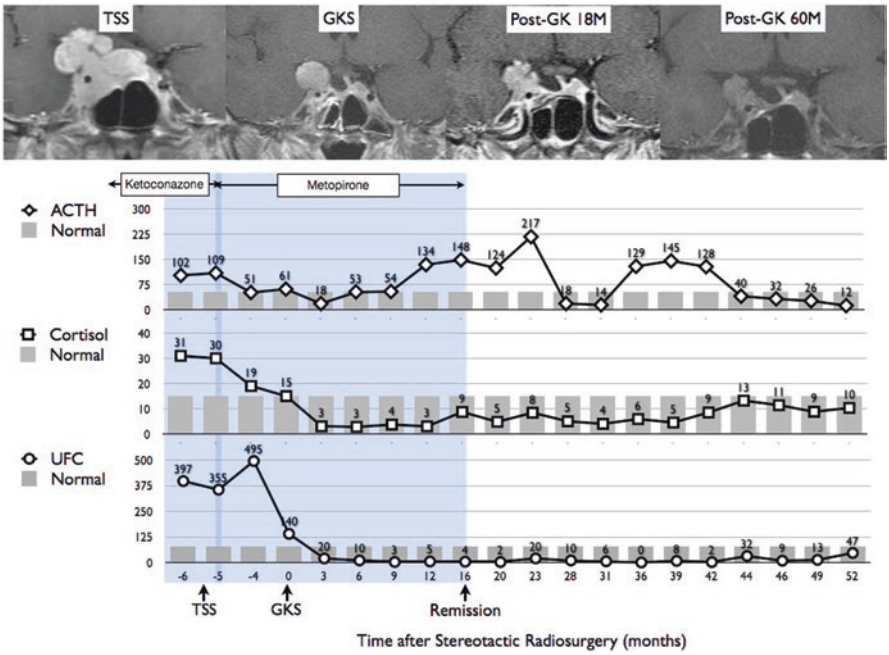

Fig. 32.3 A 45-year-old female patient with Cushing's disease underwent transsphenoidal surgery in 2010. A small residual tumor was on the right cavernous sinus. Radiosurgery was arranged for hormone and tumor control. Persistent high serum cortisol (15 ug/dL) and urine free cortisol (UFC 40 ug/24 h) levels were noted. Endocrine remission was achieved 16 months after radiosurgery. The serum cortisol and UFC were gradually decreased and suppressive medications were halted. Fortunately, the patient had no hypopituitarism during 52-month follow-up after radiosurgery (*TSS* transsphenoidal surgery, *GKS* Gamma Knife radiosurgery, *M* month)

Table 32.3 The largest six radiosurgical series for acromegaly

Study	Year	*n*	FU period (mo)	Margin dose (Gy)	Endocrine remission (%)	Hypopituitarism (%)	New onset CN deficits (%)
Castinetti et al. [9]	2005	82	50	25	17%	17%	1.2%
Jezkova et al. [23]	2006	96	54	35	54% at 54 months f/u	14–41% in various axis	0%
Losa et al. [41]	2008	83	69	22	53% at 5 years	8.5%	0%
Wan et al. [69]	2009	103	67	21	37%	N/A	N/A
Franzin et al. [14]	2012	103	71	23	58% at 5 years	7.8%	0%
Lee et al. [32]	2014	136	62	25	32, 65, 73, and 83% at 2, 4, 6, and 8 years	31.6%	1.5%

Abbreviation: *CN* cranial nerve, *Fr* fraction, *FU* follow-up, *Gy* gray, *mo* month, *NA* not available

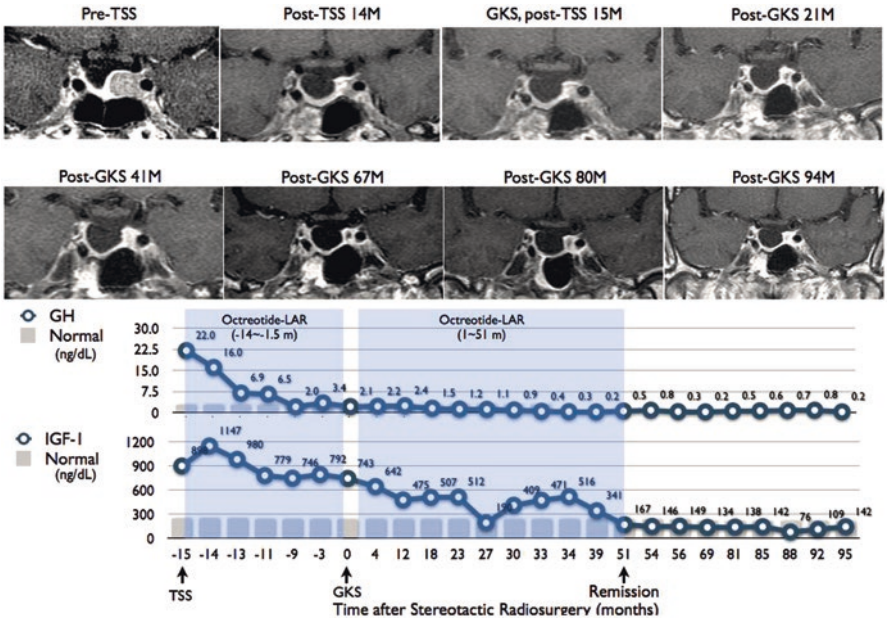

Fig. 32.4 A 54-year-old acromegaly patient with a pituitary adenoma. Although the GH decreased significantly after surgical resection, the IGF-1 was still in high level. Therefore, the SRS was arranged 15 months after surgery. Endocrine remission was achieved 51 months after SRS. He did not develop any new hormone deficiency during the 95-month follow-up after SRS (*TSS* transsphenoidal surgery, *GKS* Gamma Knife radiosurgery, *M* month)

radiosurgery for patients with acromegaly; this approach portends a greater rate of endocrine remission after SRS [40]. Figure 32.4 illustrates an acromegaly case who underwent SRS and achieved successful remission within 24 months.

For prolactinoma treated with a margin dose of 13–30 Gy, the remission rate varied from 0 to 84% [22, 26, 39, 47, 54, 66, 73]. Patients who were treated with a higher radiation radiosurgical dose had a significantly higher remission rate [39, 47, 54, 70]. In a cohort of prolactinoma patients, Witt et al. reported that no remission was achieved with a margin dose under 19 Gy [70]. Pan et al. reported a 52% remission rate and a higher margin dose of 30 Gy in a retrospective study of 128 patients in whom GKS was used as an upfront treatment for prolactinomas [27]. Although some of the reports demonstrated an acceptable outcome with a large sample size, SRS, which is used as primary treatment, is not typical in most medical centers [27]. Since prolactinomas usually respond well to medical therapy, SRS is reserved for patients with medical-refractory prolactinomas. Thus, prolactinoma patients typically undergoing SRS demonstrate a more aggressive adenoma phenotype. At the University of Virginia, only 26% of patients with medical-refractory prolactinomas achieved normalization of prolactin at a mean of 24.5 months after SRS; those off antisecretory medication at the time of SRS were more likely to achieve endocrine remission [54]. These results are also consistent with the study of Landolt and Lomax [26].

Complications

The side effects of ionizing radiation are classified as acute (within days), early delayed (within weeks), and late delayed toxicity (within months to years). Acute toxicity of stereotactic radiosurgery is rare, compared to conventional radiotherapy. Some acute radiation injuries, such as skin changes and hair loss, were rarely present in current clinical setting. The early delayed radiation injuries include hypopituitarism and hypothalamic dysfunction, radiation necrosis, new onset visual deterioration, or other cranial nerve dysfunctions. The risk of a late delayed radiation injury, which probably occurred in the era of conventional radiotherapy, is quite low when radiosurgery was applied for treating sellar tumors. Complications resulting from stereotactic radiosurgery vary depending on tumor size, the extension of tumor, and radiation doses.

Hypopituitarism and Hypothalamic Dysfunction

Hypothalamic-pituitary dysfunction is the most common intermediate to late complication of SRS of pituitary adenomas. Approximately 30–50% patients develop a new hormone deficiency, within 5–10 years after radiosurgery [15, 20, 21, 61, 62]. From the experience of SRS for pituitary adenoma in University of Virginia, 30% patients developed a delayed onset of hypopituitarism within 3 years. The thyroid function was affected most, and then gonadotrophic hormone, ACTH, and growth hormone [71]. There appeared to be two potent and independent variables, margin dose to the tumor and suprasellar extension [71], that were predictive of the risk of developing a hormone deficiency. While an ideal radiosurgical dose plan has a steep gradient index which minimizes the dose to normal pituitary tissue and therefore reduces the risk of treatment-induced hypopituitarism, a true "safe dose" below which the patient is not afflicted with hypopituitarism may not practically exist. Furthermore, an optimal radiosurgical dose to the target lesion should not be compromised for the sake of avoiding hypopituitarism. The clinical consequences of macroscopic tumor progression or recurrence or persistent hormone hypersecretion far outweigh those of radiosurgery-induced hypopituitarism which can readily be managed with medical therapy by neuro-endocrinologists.

On the other hand, very few patients have new onset diabetes insipidus (DI) after SRS, and the incidence of DI after radiosurgery is generally related to changes in the tumor complex that mechanically impact the pituitary. Other hypothalamic dysfunction including poor control of body temperature, changes in sleep and appetite are exceedingly rare event after SRS.

Cranial Neuropathy

The second most common radiosurgery-related complication following treatment of pituitary adenomas is cranial neuropathies. Multiple cranial nerves, including II, III, IV, V, and VI, by virtue of their location in the parasellar and suprasellar regions

are at risk of inadvertent injury from radiosurgical treatment. Most radiosurgery series report neurological deficit rates of less than 5% with optic neuropathy as the most common owing to its high sensitivity to radiation-induced damage [62]. In a recent study of 217 pituitary adenoma patients who underwent radiosurgery, nine patients (4%) developed new or worsened cranial nerve dysfunction. Of those patients with radiosurgery-induced cranial neuropathies, six (67%) experienced complete resolution over a median follow-up period of 32 months. If cranial neuropathies occur as a result of radiation injury, they typically do so within the first 3–5 years after SRS. Onset of such cranial neuropathies is usually quite gradual and not abrupt in onset.

The radiosurgical maximum dose to the optic apparatus should be kept below the limit threshold of 8–12 Gy in order to minimize the risk of optic nerve damage. Careful dose planning with contouring of critical structures and shielding of the same can often achieve a solution which yields delivery of an optimal dose to the target and a typically safe dose to the critical structures.

Late Adverse Radiation Effects

In the era of conventional radiotherapy, the late delayed radiation complications may include the radiation-induced secondary brain tumors and cerebrovascular disturbance when we treat sellar tumors [4–6, 45]. In the current clinical setting, the risk of a radiation-induced secondary tumor is quite low when radiosurgery was applied for treating sellar tumors. This may be due to a need for a longer latency period; however, radiobiologically, it is possible that the sharp dose fall-off achieved by stereotactic radiosurgery results in very few cells at risk for malignant transformation as compared to broader field radiation therapy approaches [7]. This hypothesis is supported by the long-term follow-up study published by Rowe [56], in which only one new primary intracranial tumor was reported among 4877 patients treated by SRS. Fortunately, there are currently no reported cases in the literature of radiation-induced neoplasm following radiosurgery for pituitary tumors.

For cerebrovascular complications, only one case has been reported of a patient who had a cerebral infarction with ICA occlusion after SRS for pituitary tumor [35].

Special Considerations and Debates

Comparison of External Beam Radiation Therapy (EBRT) Versus Radiosurgery for the Management of Pituitary Adenomas

As a result of the reported higher complications rates as well as the longer and lower success rates particularly for endocrine remission of functioning adenomas after EBRT, the current role of adjuvant, post-surgical management of recurrent or residual pituitary adenomas has largely shifted away from EBRT to radiosurgery.

While radiosurgery has displaced EBRT as the preferred adjuvant treatment modality for pituitary adenoma patients, there remain cases in which EBRT is favored. For large pituitary adenomas, typically greater than 3 cm in diameter, tumors with irregular anatomy, including diffuse local infiltration and suprasellar or brainstem extension, and lesions in very close proximity to neural structures highly sensitive to radiation (e.g., the optic apparatus), EBRT or hypofractionated SRS may represent reasonable treatment options. EBRT provides reasonable tumor control with rates exceeding 90% in most series for nonfunctioning adenomas but a lower and later rate of endocrine remission for functioning lesions with a differential response based on the adenoma subtype [13, 45]. EBRT may also be used for patients with pituitary carcinoma.

Role of Upfront Radiosurgery

As a general principle, the use of radiosurgery in the management of pituitary adenomas should be reserved for recurrent or residual lesions and for patients with functioning adenomas who remain symptomatic from persistent hormone hypersecretion despite surgical intervention. The literature does not support the routine use of upfront radiosurgery for pituitary adenomas, especially for functioning adenomas. However, radiosurgery may be used as an upfront treatment in rare and unusual circumstances. In a multicenter study enrolled the patients from University of Virginia, University of Pittsburgh, and Taipei Veteran General Hospital [30], a total of 41 patients with nonfunctioning adenoma underwent GKRS as primary management due to advanced age, multiple comorbidities, even psychiatric disorders. The overall tumor control rate was 92.7%, and the actuarial tumor control rate was 94 and 85% at 5 and 10 years post-radiosurgery, respectively. Radiosurgery could also be considered as an upfront treatment in a patient with an adenoma that residues largely in the cavernous sinus and for whom resection is unlikely to produce substantial reduction in the overall tumor volume.

Various Histological Entities of Nonfunctioning Adenomas Versus the Efficacy of SRS

Silent corticotroph pituitary adenoma represents a rare entity of nonfunctioning adenoma. Prior studies suggest that it may appear more aggressive with a high recurrent rate. At the University of Virginia, 27 consecutive patients (16% of a whole series of nonfunctioning adenoma) with silent corticotroph pituitary adenoma were identified based upon a histopathological analysis. The actuarial progression-free survival was 97, 95, and 89% in nonfunctioning group and 84, 52, and 52% in silent corticotroph pituitary adenoma group at 3, 5, and 8 years, respectively [74]. The study reflects that the silent corticotroph pituitary adenoma represents an aggressive entity with a higher recurrence rate after SRS. In view of the increased

risk of recurrence or progression, attempting to prescribe higher than the dose generally used for nonfunctioning adenomas (13–18 Gy) may be considered. This provides a critical implication regarding the use of an increased margin dose that may be required for SCA and other more radioresistant pituitary adenoma types. However, further study is required to confirm this finding.

Various Histological Entities Refine the Treatment Strategy of Functioning Adenomas

The subtypes of somatotroph-cell pituitary adenomas have been correlated with clinical and histopathological variables. Densely granulated somatotroph-cell (DG) adenomas are typically highly responsive to somatostatin analog drugs, whereas sparsely granulated somatotroph-cell (SG) adenomas are less responsive. However, while patients who had a SG adenoma may be less responsive to medical therapy, they exhibited similar responses to SRS as patients with a DG adenoma. Therefore, for SG adenomas, earlier SRS may be reasonable for consideration [31].

The results came from a total of 176 patients who underwent SRS for acromegaly at the University of Virginia, and histological specimens were available in 73 patients [31]. Patients who had a SG adenoma were more likely to be younger and female and the SG adenomas appeared to be more invasive into the cavernous sinus. The actuarial remission rates in the DG adenoma group at 2, 4, and 6 years post-radiosurgery were 35.1, 71.4, and 79.3%, respectively, while those in SG adenoma group were 35.4, 73.1, and 82.1%, respectively.

The Apparent Radioresistant Effects of Antisecreting Medications

The negative effect of somatostatin analogs on the results of SRS for acromegaly was first reported in 2000 [26, 53]. Landolt and colleagues detailed the influence of octreotide on the results of SRS in 31 patients. They found that patients treated with octreotide at the time of SRS achieved a normal level of growth hormone and IGF-1 after a significantly longer interval than patients who did not receive the drug [26]. Pollock et al. also reported similar results in 2002 [53]. The similar condition also occurred in the patients with prolactinomas: the remission rate was in patients receiving an antisecretory medication at the time of radiosurgery [27]. As a result of these studies, it is generally recommended to discontinue antisecreting medications for approximately 6 weeks before SRS and resume them 2–6 weeks after SRS. Similar findings of deleterious effects from ketoconazole after SRS for Cushing's disease patients have been found [63]. Larger, randomized clinical trials are still necessary to confirm the negative relationship between hormone-suppressive medications and outcome of radiosurgery.

Whole-sellar SRS for MR Indeterminate Functioning Adenomas

The concept of the whole-sellar SRS comes from the total and partial hypophysectomies for the MRI-negative but hormone-active Cushing's disease. Although being the best neuro-imaging study for defining pituitary adenomas, MRI has been reported to fail to detect between 36 and 64% of patients with ACTH-secreting pituitary adenomas [42]. On the other hand, the patients frequently have residual tumor with microscopic infiltration of the venous sinuses or adjacent dura and are neither readily evident on neuro-imaging studies nor surgical accessible. As a result, recurrence rates for Cushing's disease have been reported to range from 5 to 27% with a mean follow-up period ranging from 6.7 to 9.6 years [10, 18, 64, 72]. Based on the considerations above, the whole-sellar SRS appears to be a reasonable approach for selected patients. At the University of Virginia, we delivered radiosurgery to the entire sella for symptomatic patients with a medically refractory, invasive, or imaging-negative functioning pituitary adenomas [29]. Adopting a similar rationale of hypophysectomy, whole-sellar SRS attempts to treat recurrent or persistent diseases by delivering focused high-dose radiation to the entire sellar and parasellar contents, since microscopic invasion can be neither localized on imaging studies nor identified by surgeons intra-operatively. Endocrine remission of 54, 78, and 87% was achieved within 2, 4, and 6 years after SRS, respectively. We observed hypopituitarism in 42.2% of the patients with 3.1% eventually developing panhypopituitarism during the follow-up period. Compared to the morbidities of persistent hypersecretion from a functioning adenoma, patients with post-radiosurgery hypopituitarism can be readily and fully treated with hormonal replacement. Therefore, whole-sellar SRS could be an effective treatment for functioning adenoma patients without a discrete adenoma on MRI [29].

Conclusions

Radiosurgery plays an important role in the contemporary management of patients with a pituitary adenoma. SRS is typically used in patients with substantial residual tumor or recurrence after surgical resection of nonfunctioning adenomas. SRS is also employed for patients with functioning adenomas that fail to achieve endocrine remission after prior resection. Neurological function after radiosurgery is usually preserved or, at times, improved even when the treated adenoma extends into the cavernous sinus. Delayed post-radiosurgical hypopituitarism is the most common complication but is manageable with appropriate hormone replacement. Long-term neuro-imaging and endocrine follow-up is recommended for pituitary adenoma patients treated with radiosurgery.

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Radiation Therapy for Pituitary Tumors

33

Trevor J. Royce, Jay S. Loeffler, and Helen A. Shih

Introduction

Radiation has been used as a treatment modality for pituitary adenomas for almost half a century and can be highly effective at preventing tumor growth as well as resolving pituitary adenoma hypersecretion. Literature reporting the successful use of radiation therapy for pituitary adenomas is generally presented as retrospective series using a single radiation technique. Challenges can therefore arise when comparing the different radiation modalities described in detail below. This is particularly problematic when examining functioning adenomas and the endocrine response to radiation, as there are no standardized response criteria [1]. These challenges are magnified by nonstandardized radiation doses and biochemical assays.

Modalities of Radiation Therapy

Fractionation

Radiation therapy for a pituitary tumor is generally delivered via one of the two techniques: stereotactic radiosurgery (SRS) or fractionated (conventional) radiation. Stereotactic radiosurgery typically consists of a single high-dose treatment of radiation delivered using a precise localization system. Modalities that employ this technique include Gamma Knife, CyberKnife, linear accelerator-based stereotactic radiosurgery, and proton radiation therapy. Radiosurgery is convenient, typically safe, equivalently effective, and generally preferred for small targets (e.g., tumors less than 3 cm). SRS may also have a more rapid reduction in supraphysiological

T.J. Royce, MD MS • J.S. Loeffler, MD • H.A. Shih, MD, MS, MPH (✉)
Harvard Medical School, Department of Radiation Oncology,
Massachusetts General Hospital, Boston, MA, USA
e-mail: jloeffler@partners.org; hshih@partners.org

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_33

hormone levels; nonrandomized studies have shown that the average time required for hormone normalization is less for SRS compared to fractionated radiation [2, 3].

Conventional fractionated radiation is delivered via photons with a linear accelerator or protons and typically consists of smaller doses of radiation delivered in 25 to 30 daily treatments over 5–6 weeks. Across all indications for radiotherapy, fractionated radiation is the most common way of delivering radiation and is the most accessible modality. For pituitary adenomas, this approach is generally favored for larger tumors and tumors in close proximity, 3–5 mm or closer and if abutting, to at-risk radiation-sensitive normal tissues, such as the optic chiasm. While radiosurgery in this setting could result in blindness, the amount of fractionated radiation required to control a pituitary adenoma is generally within the tolerance of the surrounding normal tissues, making it a safe and effective alternative to SRS. Conventional treatment thus has a lower risk of normal tissue injury but may be less convenient.

Gamma Knife Radiosurgery

Stereotactic radiosurgery was invented in 1951 by the team led by Swedish neurosurgeon Lars Leksell. By the 1960s, these pioneers had developed the Gamma Knife (GK; Elekta, Stockholm, Sweden) and were applying stereotactic radiosurgery in the clinical setting [4]. The GK was initially used to treat arteriovenous malformations and trigeminal neuralgia in a noninvasive fashion but has since been widely adopted to treat a variety of small intracranial targets including brain metastases, vestibular schwannomas, and pituitary adenomas. GK is well established and has the most experience of the radiosurgical techniques used to treat pituitary tumors. In the GK, gamma rays, also known as photons, are produced via the radioactive decay of cobalt-60, a radioactive isotope that has a half-life of 5.5 years and produces photons with an average energy of 1.25 MV. In the current design, a total of 201 cobalt-60 sources are housed in the GK machine. Stereotaxy is achieved with a metal headframe that is fixed to the patient's head and the treatment machine. Bores of varying diameter in the machine frame determine the number and width of the radiation beams being emitted from a selected subset of the 201 cobalt-60 sources, resulting in multiple tiny beams of radiation which intersect on the desired intracranial target to create a conformal dose cloud. The low megavoltage energy allows for limited tissue penetration in the head, minimizing dose to normal bystander tissues. A steep radiation dose fall-off creates a high-dose gradient between the target, which receives the full dose, and normal tissues, which receive negligible dose. The dose gradient is such that on average the periphery of the target receives half the dose delivered to the target's geometric center. The frame is fastened to the head with minimally invasive screws which penetrate the skin and anchor on the skull. The latest version of the GK utilizes a facemask immobilization technique that avoids the invasive screws, making for a more pleasant patient experience and the ability to provide fractionated treatment. For the sake of convenience and patient comfort, the treatments are therefore usually performed in a single outpatient visit.

Linear Accelerator-Based Stereotactic Radiosurgery

A linear accelerator (LINAC) is the most commonly used device for external beam radiation therapy. It is a sophisticated machine which accelerates electrons to a high speed and then converts that energy into a beam of x-rays, also known as photons. That beam is then attenuated, shaped, and aimed at a clinical target. Multiple radiation beams are used for treatment, sometimes using arcs of noncoplanar beams and circular collimators to deliver a conformal dose [4]. An arc is when radiation is continuously delivered as a machine moves around a central axis at a fixed diameter. This system has been modified to use a stereotactic targeting system, a technique which allows precise localization using a three-dimensional coordinate system with sub-millimeter accuracy. LINAC-based SRS has been shown to be as efficacious as GK when treating pituitary adenomas [2, 5]. Similar to the GK, LINAC SRS is the delivery of high doses of radiation in a single treatment. Setup for these treatments involves a stereotactic frame which is fixed to the patient's head and the LINAC patient platform. One technique is to fix the stereotactic frame to the patient's head with a noninvasive dental mold. A radiation planning session, or simulation, is then performed. This planning session involves obtaining a CT scan with the patient in the treatment position. MRI scans are sometimes fused to the CT data to aid in target delineation and treatment planning. LINAC-based SRS can achieve reduced dose hotspots, or areas receiving radiation above the prescribed dose, and provide a more homogenous dose distribution than that of GK. The arcs of radiation move around a central axis which results in a spherical or ellipsoid dose distribution, sometimes at the sake of conformality when treating irregularly shaped targets.

Fractionated Radiation Therapy

Fractionated radiation therapy has conventionally been delivered in a three-dimensional conformal method with a LINAC. This modality has the greatest current clinical implementation in treatment of pituitary adenomas as it is the most widely available. A CT-based planning method is employed but immobilization and planning systems are sometimes used that have the potential to introduce greater error and uncertainty in dose delivery and patient setup. Treatment setup is done with a custom-made thermoplastic facemask which molds to the patient's facial contour and is fastened directly to the LINAC patient platform. Like all forms of immobilization, the mask aims to keep the head in the same position for each treatment, minimizing the day-to-day treatment variability in patient positioning. Because this technique can have a greater setup error than in a stereotactic treatment, this modality uses slightly larger planning target coverage margins incorporated into the treatment fields to ensure delivery of dose to the target volume. Three-dimensional conformal radiation planning typically uses a range of 2–5 treatment fields. The concept of fractionation is applied in a variety of more advanced radiation therapy techniques, such as intensity-modulated radiation therapy or stereotactic radiotherapy, both treatment delivery adaptation techniques using the

LINAC, which can be employed to minimize high-dose exposure to surrounding normal tissues. The term stereotactic radiotherapy (SRT) is used when LINAC-based stereotactic treatment is delivered in fractionated doses with a stereotactic immobilization system. Fractionated radiation for pituitary adenomas typically consists of SRT delivered with doses of 1.8–2.0 Gy per treatment, a fraction size classically applied to other disease sites across radiation therapy. The term "hypofractionation" is sometimes used for treatment schemes using higher doses per fraction. Although far less common in use, both proton therapy and CyberKnife can also be used to deliver fractionated radiation therapy.

CyberKnife

CyberKnife (Accuray, Sunnyvale, CA) is a frameless robotic radiosurgery system that was created by Stanford University neurosurgeon John Adler in the 1980s. The CyberKnife has a small linear accelerator mounted to a robotic arm and delivers image-guided radiation without the use of a headframe. The robotic arm applies real-time image-guided adjustments to correct for variability in patient setup resulting in sub-millimeter accuracy. It delivers numerous small beams of radiation resulting in a highly conformal dose distribution. Overall treatment times are generally longer than other radiation modalities. The device can deliver dose as a single large radiosurgery or as fractionated radiation over many treatments.

Proton Therapy

As the name suggests, proton beam therapy is a particle therapy which uses a beam of accelerated protons, the nucleus of hydrogen atoms, to deliver energy to a target. A beam of high-energy proton particles is accelerated by a cyclotron or synchrotron and then undergoes a series of modifications and manipulations before ultimately being delivered to the target. Unlike photons, protons possess mass and charge which give them unique dose-depositing properties. The biological effects of the dose deposited, however, is similar. Protons deposit most of their ionizing radiation at the Bragg peak, the point at which the protons penetrate deepest in tissue. This creates a sharp dose fall-off at a specified depth in tissue, minimizing the radiation exposure of normal tissues beyond the target. The Bragg peak can be manipulated to achieve a conformal dose distribution on the target. Minimizing the exposure of normal tissues to ionizing radiation may decrease the risk of radiation-related complications. This is a priority when treating benign conditions, such as pituitary adenomas, where the goal of therapy is to maintain a normal life expectancy. The concept of proton therapy has been around since the 1940s and reports regarding the efficacy of proton therapy for pituitary tumors have been published since the 1960s [6]. However, building a proton facility remains an expensive and complex undertaking; this has limited the number of proton centers in the world. It remains a scare resource, but the attractive benefits of this modality combined with

continued technological advancements have resulted in a surge of planned proton therapy centers. Proton radiation can be used to treat pituitary adenomas in a single fraction via SRS or in a conventionally fractionated approach.

Nonfunctioning Adenomas

Nonfunctioning pituitary adenomas are pituitary tumors that do not produce excess levels of pituitary hormones. Presentation results from symptoms related to mass effect, and the goal of radiation therapy is to prevent further growth of the tumor. Symptom relief can occur if the mass shrinks. Shrinkage rates of up to 66% have been observed in GK SRS series [7, 8]. Radiation should be administered as the primary therapy in medically inoperable patients or preferentially considered in the adjuvant setting for subtotal resections that often occur when there remain surgically inaccessible tumors (e.g., involvement of the cavernous sinus). The historical standard of care has been surgical decompression followed by immediate postoperative radiation, which decreases the risk of recurrence [9]. Adjuvant radiation has risks, such as hypopituitarism, and studies have examined the necessity of adjuvant radiation following complete macroscopic resection. It has largely been found that salvage RT can effectively be employed in the case of recurrence, the risk of which is in the range of 0–15% at 5 years following a gross total resection [9–15]. Recurrences can be detected early with modern imaging and close follow-up and effectively managed in the salvage setting [9, 10]. Salvage versus adjuvant radiation will therefore spare most patients from radiation exposure following a gross total resection and can delay radiation-induced side effects, should radiation ultimately be needed in the event of a recurrence. Therefore, adjuvant radiation therapy is now not generally indicated following gross total resection.

Untreated residual tumor following resection places the patient at risk for recurrent or new symptoms as subtotal resections have much higher rates of recurrence and should be considered for adjuvant radiation therapy. Studies have shown recurrence rates of around 40–60% at 5 years for patients treated with subtotal resection alone. Tumor involvement outside the sella, the cavernous sinus in particular, is predisposing to recurrence [13–17]. Those patients not treated with adjuvant radiation therapy should be on regular surveillance, typically with annual imaging, to ensure lack of progression. Radiation therapy can be subsequently employed at time of tumor progression with high tumor control success and delay in potential radiation-related toxicities. Stratifying patients with a subtotal resection of nonfunctioning pituitary adenomas by risk of recurrence based on pathologic and molecular markers of tumor proliferation may eventually allow for the more judicial application of post-resection radiation [18, 19].

Nonfunctioning pituitary adenomas have successfully been treated with single-fraction SRS or conventionally fractionated radiation and using photons or protons. The most common SRS fraction sizes range from 12 to 20 Gy, with 16–18 Gy being preferred (Table 33.1). Local control is generally greater than 90%, irrespective of

Table 33.1 Radiation therapy for nonfunctioning pituitary adenomas

First author, year (Ref.)	Study years	RT type	RT dose (Gy), median (range)	*N*	Follow-up, median (years)	LC (%)	LC median (years)	New endocrinopathy after RT (%)
Brada, 1993 [66]	1962–1986	Conv	45 (45–50)	252		88	20	50 at 19 years
Tsang, 1994 [74]	1972–1986	Conv	45 (40–50)	128	8.3	91	10	>23
Colin, 2005 [26]	1990–1999	SRT	50.4	63	6.8	100	6.8	60 at 8 years, estimate
Iwai, 2005 [75]	1994–1999	GK	14 (8–20)	34	5	93	5	6.5 at 5 years
Mingione, 2006 [8]	1989–2004	GK	18.5 mean (5–25)	90	3.7	92		25 at 3 years
Ronson, 2006 [53]	1991–2001	Protons	54 (50.4–55.9)	24	3.9	100		44 at 10 years
Voges, 2006 [39]	1990–2004	L-SRS	13.4 mean (8–20)	37	4.7, mean	100		18 at 5 years
Liscak, 2007 [20]	1993–2003	GK	20 (12–35)	140	5	100		6.7 at 7 years
Van den Bergh, 2007 [61]	1979–1998	Conv	45 (45–55.8)	76	7.8	95	10	36
Chang, 2008 [13]	1975–1995	Conv	45 (45–54)	340	8.4	74	20	
Pollock, 2008 [7]	1992–2004	GK	16 (11–20)	62	5.3	95	7	32 at 5 years
Snead, 2008 [76]	1983–2003	Conv	45 (43–50.4)	59	6.7	98	10	35
Erridge, 2009 [21]	1974–2003	Conv	45 (35–60)	189	9.1	95	10	>28 at 10 years
Sheehan, 2011 [22]	1989–2006	GK	24 (9–30)	152	2.6	90		22 at 5 years

RT radiation therapy, *N* number of patients, *LC* local control, *L-SRS* linear accelerator-based stereotactic radiosurgery, *GK* Gamma Knife radiosurgery, *Conv* conventional fractionated radiation therapy, *SRT* fractionated stereotactic radiation therapy

the radiation modality employed. One series looking at 140 patients treated with GK SRS treated with a median dose of 20 Gy found local control to be 100% at a median follow-up of 5 years [20]. Fractionated doses range from 45 to 54 Gy at 1.8 Gy per fraction, usually 45–50.5 Gy, and demonstrate excellent local control (Table 33.1). One retrospective series looking at 340 patients treated with surgery and fractionated radiotherapy to 45–54 Gy had local control rates at 5 years of greater than 90% [13].

Choosing SRS versus conventional fractionation depends primarily on the size of the lesion and if the high, single-fraction dose of SRS can be administered without putting critical normal tissues at risk. Tumor involving or in close proximity to important structures such as cranial nerves or components of the optic tract may be best addressed with fractionated radiation due to lower rates of normal tissue complications [2, 21]. For example, tumors near the optic chiasm or exhibiting extension into the cavernous sinus are candidates for conventional fractionation. Radiosurgery is preferred if the normal critical structures can be safely spared, such as in the instance of an adenoma greater than 3–5 mm from the optic pathway and less than 3 cm in diameter [20, 22].

Functioning Adenomas

Functioning adenomas are pituitary tumors that produce excess levels of pituitary hormones, which can result in a syndrome specific to the hormone overproduced. Symptoms also result from mass effect, as is the case in nonfunctioning pituitary adenomas. Thus, the goal of therapy is twofold: to decrease levels of excess hormone and to arrest tumor progression. Functioning adenomas are categorized based on the hormone they overproduce and include corticotroph adenomas (Cushing's disease), somatotroph adenomas (acromegaly), lactotroph adenomas (prolactinoma), and other functional adenomas. Radiotherapy is most often employed when these tumors are refractory to surgical and/or medical management with persistently poor hormonal or growth control.

These tumors can be treated with both SRS and fractionated radiation therapy. As aforementioned, SRS may achieve more rapid hormone normalization [2, 3]. Tumor less than 3 cm in size and greater than 3 mm in distance from the optics are excellent candidates for radiosurgery; fractioned RT can be utilized in any adenoma and is preferred in larger tumors close to critical structures [23, 24]. Treatment with radiation is effective: the local control is greater than 90% and a complete or partial hormonal response is achieved in 60–80% of patients [1, 25, 26]. In the setting of a partial hormonal response, medical therapy can be used in conjunction to achieve optimal results. Smaller secretory adenomas are correlated with improved hormonal control and better preservation of pituitary function, illustrating the utility of upfront debulking surgery [22, 27–30]. It is also generally recommended to discontinue centrally acting medical management 1 month prior to radiation and not resuming until after radiation is completed, as hormonal response to radiation therapy appears to be improved

in the absence of medical therapy [22, 27, 28, 31]. One study of 418 patients even found an association between the use of medical therapy with radiation therapy and an increased risk of iatrogenic hypopituitarism [22].

Corticotroph Adenomas (Cushing's Disease, ACTH-Secreting Pituitary Adenomas)

Corticotroph adenomas refractory to surgical and medical management should be considered for radiation therapy. The goals of therapy are local control and, importantly, control of ACTH secretion. SRS with a single fraction of 15–30 Gy (20–25 Gy is preferred for optimal balance of safety and efficacy) is used if the tumor is at an acceptable distance from the critical normal structures. For larger adenomas near critical normal structures, fractionated radiation to 45–60 Gy (50.4–54 Gy is preferred for safety and efficacy) is used [22, 23, 32–37]. Radiation produces excellent local rates greater than 90% across radiation modalities, similar to those seen with nonfunctioning adenomas [22, 32, 33, 35].

Radiation is also effective at hormone control, achieving normal cortisol levels in approximately 50% of patients by 5 years; this efficacy is similar across radiation modalities [2, 22, 27, 30, 32, 33, 35–38]. Hormone levels in patients with ACTH-secreting adenomas treated with SRS may normalize faster than those treated with fractionated RT, with median normalization times of 7.5–33 months (Table 33.2). SRS is more efficient with a single day of treatment versus the 5–6 weeks of daily treatments used in fractionated RT. Some studies do not report on the use of medical therapy, making comparison of hormone normalization rates across studies a challenge, but modern SRS series of 15 or more patients suggests rates between 35 and 80% at 2–8 years. Conventional radiation with modern techniques also have hormone control rates of 50–80% by 3–9 years and a median time to cortisol normalization of 1.5–3.5 years (Table 33.2).

There is limited data regarding the efficacy of radiation therapy when treating Nelson's syndrome, the enlargement and increased activity in a corticotroph adenoma following a bilateral adrenalectomy. Some series suggest Nelson's syndrome may be less responsive to radiation but the data are conflicting with small sample sizes [22, 30, 36, 37, 39].

Somatotroph Adenomas (Acromegaly, Growth Hormone-Secreting Pituitary Adenoma)

As with corticotroph adenomas, radiation can be used when the somatotroph adenoma is refractory to the first-line therapy of surgery. Radiation provides the potential for cure while medical management may be a lifelong commitment. The goal of treatment is to address both excess hormone production and mass effect from adenoma growth. Hormone and local control rates are similar with SRS versus conventional radiation therapy, and the choice of treatment modality depends on the tumor

Table 33.2 Radiation therapy for corticotroph adenomas

First author, year (Ref.)	Study years	RT type	RT dose (Gy), median (range)	N	Follow-up, median (years)	LC (%)	LC median (years)	Hormone normalization (% CR)	Hormone normalization time, median (years)	New endocrinopathy after RT (%)
Estrada, 1997 [34]	1980–1993	Conv	50, mean (48–54)	30	4.6, mean			83	1.5, mean	57
Mitsumori, 1998 [2]	1989–1995	SRT SRS	45 15 (10–18)	2 5	2.8 3.9	85 100	3 3	54 33	1.5, mean 0.7, mean	20 at 3 years 23 at 3 years
Höybye, 2001 [38]	1976–1985	GK	140 (60–240)	18	17, mean	100		83		100 at 10 years
Kobayashi, 2002 [30]	1991–1999	GK	28.7 (15–70)	20	5.3, mean	100		35		
Devin, 2004 [32]	1991–2002	L-SRS	15 (7–33)	35	1.9	91	1.8	37	0.6, mean	40 at 10 years
Colin, 2005 [26]	1990–1999	SRT	50.4	10	6.8	100	6.8	100		60 at 8 year, estimate
Ronson, 2006 [53]	1991–2001	Protons	54 (50.4–55.9)	4	3.9	100		25		44 at 10 years
Voges, 2006 [39]	1990–2004	L-SRS	16.4 mean (8–20)	17	4.9, mean	88		78	2.4, mean	18 at 5 years
Castinetti, 2007 [27]	1993–2003	GK	29.5 (15–40)	40	4			43	1.8, mean	15 at 10 years
Jagannathan, 2007 [33]	1990–2005	GK	25	90	3.8	96		54	1.1, mean	87 at 3 years
Minniti, 2007 [35]	1988–2002	Conv	45 (45–50)	40	9	93	10	84	2, mean	>51 at 10 years
Castinetti, 2009 [51]	1993–2003	GK	28, mean (16–35)	18	8, mean	100		50	2.3, mean	21 at 6 years
Sheehan, 2011 [22]	1989–2006	GK	24 (9–30)	82	2.6	90		54	1.1	22 at 5 years
Wattson, 2014 [37]	1992–2012	Protons	20 (15–24) 50.4–54	79	4.3	98	3.6	67	2.7	62 at 5 years

RT radiation therapy, *N* number of patients, *LC* local control, *L-SRS* linear accelerator-based stereotactic radiosurgery, *GK* Gamma Knife radiosurgery, *Conv* conventional fractionated radiation, *SRT* fractionated stereotactic radiation therapy, *CR* complete response

characteristic of size and proximity to critical structures, such as the optic apparatus, which are less tolerant to SRS fractionation schemes. SRS doses of 10–35 Gy in a single fraction (20–25 Gy is preferred for safety and efficacy) or 40–54 Gy (50.4–54 Gy in 1.8 Gy fractions is preferred for safety and efficacy) of fractionated RT have been commonly employed [22, 39–43]. This is summarized in Table 33.3.

Comparing hormonal response rates to RT across studies is challenging in the absence of standard response metrics. Endpoints defining remission and hormone normalization vary and are confounded by the variable use of medical management. Complete remission is often defined as GH levels between 1.7 and 5 ng/ml. Insulin-like growth factor-1 (IGF-1) and oral glucose tolerance test normalization may or may not be included in the analysis. In spite of these limitations, SRS does appear equally efficacious in achieving hormone normalization across modalities, including protons [37, 44], GK [22, 27, 31, 40, 41, 45, 46], CyberKnife [29], and linear accelerator-based SRS [39, 47] (Table 33.3). Unlike the rapid hormone normalization one would expect with surgery, it takes time on the order of years for normalization following RT. Approximately 50–60% of patients have growth hormone and insulin-like growth factor concentrations normalize at 5–10 years and 65–87% at 15 years (Table 33.3) [22, 39–43, 48, 49]. The median time to remission with SRS ranges from 3 to 10 years and is slightly quicker than conventional fractionation, which ranges from 6 to 10 years (Table 33.3). This wide range of time to remission is likely a reflection of the varying response metrics and endpoints used across studies. Patients with lower pre-treatment hormone levels appear more likely to achieve satisfactory hormonal control [42, 48]. As with corticotroph adenomas, radiation is highly effective for local control of somatotroph adenomas with rates greater than 90%, regardless of modality [39–41, 43].

Lactotroph Adenomas (Prolactinoma, Prolactin-Secreting Pituitary Adenoma)

Unlike other functional pituitary adenomas, medical management is the first-line therapy for prolactinomas. Dopamine agonists are efficacious with rapid onset, achieving hormone normalization rates of nearly 90% [50]. Those that fail can then usually be addressed with surgical management or a combination of medical and surgical management, so the need for radiation is uncommon. Because of effective medical therapy, the goal of radiation is usually local control. Radiation is a curative therapy, useful in those patients with persistent disease who are medically inoperable. SRS [28, 39, 51, 52] and conventional fractionation [21, 53] appear equally effective in achieving local control, with rates greater than 90% (Table 33.4). As with other pituitary adenomas, the preferred radiotherapeutic modality depends on the size and location of the tumor; SRS is used when possible, given the convenience of being treated with a single fraction.

Hormone normalization generally occurs in up to 50% of prolactinomas with radiation alone. Series show SRS achieves hormone normalization rates at 2–8 years of 15–50% and up to 40–80% with the addition of medical therapy (Table 33.4)

Table 33.3 Radiation therapy for somatotroph adenomas

First author, year (Ref.)	Study years	RT type	RT dose (Gy), median (range)	N	Follow-up, median (years)	LC (%)	LC median (years)	Hormone normalization (% CR)	Hormone normalization time, median (years)	New endocrinopathy after RT (%)
Landolt, 1998 [3]	1973–1992 1994–1996	Conv GK	40 (40–56) 25	50 16	7.5, mean 1.4, mean	100 100		80, est. 70, est	7.1, mean 1.4, mean	16 0
Barrande, 2000 [48]	1951–1998	Conv	52 (43.5–60.5)	128	11.5, mean			66		>34 at 10 years
Powell, 2000 [47]	1981–1999	Total Conv GK L-SRS Protons	47.4, mean (45–54) 48, mean (44–53) 28, mean (18–30)	43 32 4 6 1	5.2, mean			40 43 0 50 0	5.6, mean 1.2, mean 2.9, mean 3.6	32
Cozzi, 2001 [77]	1971–1993	Conv	46 (19–75)	49	14	96		16		>12 at 5 years, est
Epaminonda, 2001 [78]	1969–1996	Conv	53.6, mean (40–75)	67	10			65		60 at 20 years
Colin, 2005 [26]	1990–1999	SRT	50.4	31	6.8	100	6.8	29		60 at 8 year, est
Minniti, 2005 [62]	1982–1994	Conv	45 (45–50)	47	12	95	15	83		>52 at 15 years
Jenkins, 2006 [42]	1970–2004	Conv	45 (10–55)	656	7			77	10, mean	>18 at 10 years
Jezkova, 2006 [41]	1993–2003	GK	35 (10–42)	96	4.5, mean	100		86		>31 at 6 years
Ronson, 2006 [53]	1991–2001	Protons	54 (50.4–55.9)	11	3.9	100		45		44 at 10 years
Voges, 2006 [39]	1990–2004	L-SRS	16.5, mean (8–20)	64	4.5, mean	97		33	3.6, mean	18 at 5 years
Jallad, 2007 [43]	1978–2003	Conv	50, mean (32.4–60)	89	4	100		54	3.8, mean	47
Pollock, 2007 [31]	1991–2004	GK	20 (14.4–30)	46	5.3	100		50	3	33 at 5 years

(continued)

Table 33.3 (continued)

First author, year (Ref.)	Study years	RT type	RT dose (Gy), median (range)	N	Follow-up, median (years)	LC (%)	LC median (years)	Hormone normalization (% CR)	Hormone normalization time, median (years)	New endocrinopathy after RT (%)
Roberts, 2007 [29]	1998–2005	CK-SRS	21 (18–24)	9	2.1, mean	100	2.1	44	1, mean	33
Vik-Mo, 2007 [45]	1989–2002	GK	26.5 (12–35)	53	5.5, mean	100		86		18 at 10 years
Losa, 2008 [40]	1994–2006	GK	21.5 (20–25)	83	5.8	98		85		9
Castinetti, 2009 [51]	1993–2003	GK	28, mean (16–35)	43	8, mean	100		42	4.2, mean	21 at 6 years
Ronchi, 2009 [79]	1995–2004	GK	20 (15–35)	35	9.5	100	10	43	10.8, mean	50 at 10 years
Iwai, 2010 [46]	1995–2005	GK	20 (14–30)	26	7	96		47		8 at 11 years
Sheehan, 2011 [22]	1989–2006	GK	24 (9–30)	130	2.6	90		53	2.5	22 at 5 years
Wattson, 2014 [37]	1992–2012	Protons	20 (15–24) 50.4–54	61	4.3	98	3.6	49	5.2	62 at 5 years

RT radiation therapy, *N* number of patients, *LC* local control, *L-SRS* linear accelerator-based stereotactic radiosurgery, *GK* Gamma Knife radiosurgery, *CK-SRS* CyberKnife SRS, *Conv* conventional fractionated radiation, *SRT* fractionated stereotactic radiation therapy, *CR* complete response, *est* estimate

Table 33.4 Radiation therapy for lactotroph adenomas

First author, year (Ref.)	Study years	RT type	RT dose (Gy), median (range)	N	Follow-up, median (years)	LC (%)	LC median (years)	Hormone normalization (% CR)	Hormone normalization time, median (years)	New endocrinopathy after RT (%)
Tsagarakis, 1991 [80]	1972–1981	Conv	45	36	8.5			50	7.3, mean	>78 at 12 years
Tsang, 1996 [55]	1972–1986	Conv	50 (40–52)	64	7.3	96	10	25	10	>35 at 10 years
Pan, 2000 [54]	1993–1997	GK	31.2, mean (9–35)	128	2.8, mean	98		52		
Sasaki, 2000 [81]	1969–1994	Conv	51 (44–70)	6	8.2	80		80		>50
Colin, 2005 [26]	1990–1999	SRT	50.4	4	6.8	100	6.8	25		60 at 8 years, est
Pouratian, 2006 [28]	1990–2003	GK	18.6 (0.3–25)	23	4.6	89		26	2	28 at 4 years
Ronson, 2006 [53]	1991–2001	Protons	54 (50.4–55.9)	6	3.9	100		33		44 at 10 years
Voges, 2006 [39]	1990–2004	L-SRS	13.5, mean (8–20)	13	4.7, mean	100		17	4, mean	18 at 5 years
Castinetti, 2009 [51]	1993–2003	GK	28, mean (16–35)	15	8, mean	100		46	2, mean	21 at 6 years
Erridge, 2009 [21]	1974–2003	Conv	45 (35–60)	58	9.1	95	10			>28 at 10 years
Jezkova, 2009 [52]	1993–2005	GK	34 (20–49)	35	6.4, mean	97		80	8	>14 at 8 years
Sheehan, 2011 [22]	1989–2006	GK	24 (9–30)	32	2.6	90		26	2	22 at 5 years
Wattson, 2014 [37]	1992–2012	Protons	20 (15–24) 50.4–54	12	4.3	98	3.6	38	5	62 at 5 years

RT radiation therapy, *N* number of patients, *LC* local control, *L-SRS* linear accelerator-based stereotactic radiosurgery, *GK* Gamma Knife radiosurgery, *Conv* conventional fractionated radiation, *SRT* fractionated stereotactic radiation therapy, *CR* complete response, *est* estimate

[22, 28, 39, 51, 52, 54]. Normalization with SRS may take longer for prolactinomas than for other secretory adenomas, and many of these patients are treated with a dopamine agonist until radiation-induced biochemical normalization occurs [54, 55]. The data using fractionated radiation (usually 45–54 Gy) are more limited but demonstrate outcomes comparable to SRS, with hormone normalization rates at 1–10 years of 25–50% and up to 80–100% with the addition of medical therapy (Table 33.4). A limitation in interpreting these data is that hyperprolactinemia itself is not necessarily an indication for treatment, limiting its utility as a clinical endpoint. More important are the clinical symptoms, such as hypogonadism, which may be successfully addressed medically [50].

Other Pituitary Adenomas

Experience with management of other types of pituitary adenomas, including gonadotropic adenomas (luteinizing hormone-secreting or follicle-stimulating hormone-secreting adenomas) and thyrotropic adenomas (thyroid-stimulating hormone-secreting adenomas), is limited and sparsely reported. These tumors are rare; thyrotropic adenomas account for only 0.5–3% of functioning pituitary tumors [56]. Most series contain less than ten patients. Treatment is deduced from experience with other functional pituitary adenomas. Local control appears to remain excellent and hormonal control may be achieved in approximately 50% of patients [39, 57].

Radiation-Related Adverse Effects

Radiation is a local treatment, and the adverse effects caused by pituitary irradiation are largely dictated by structures near the target. The technology of radiation therapy has advanced dramatically in the past 25 years, greatly improving the accuracy of high-dose radiation delivery to the target while providing steep dose gradients at the border of the target, minimizing the radiation exposure to normal, bystander tissue. Improved conformality and reduced treatment field size all help decrease the risk of radiation-related toxicity. In spite of this, adverse effects do still occur. These adverse effects are usually not thought of as reversible and the risk of adverse effects generally increase as the number of years from radiation treatment increases; they usually are not seen in the first 5 years after treatment. This is in contrast to surgery, where adverse effects are generally evident upfront and may improve in time. Visual deficits, neurologic symptoms, and secondary tumors are rare; there is even data to suggest that patients who receive radiation therapy for the pituitary adenoma may have better physical and mental health than equivalent patients treated with surgery alone [58]. The true incidence of the late adverse effects from radiation will not be known until there exists longer follow-up in patients treated with modern radiation techniques, but one would expect them to be less than historical controls.

Hypopituitarism

Hypopituitarism is common and occurs regardless of the modality or fractionation of radiation; it is the most common adverse effect of pituitary adenoma irradiation. Most patients will develop a deficiency in one or more anterior pituitary hormones; the risk of a deficiency increases with time. Thyrotropes, corticotropes, and gonadotropes are all affected and single or multiple hormonal axes can be impacted. Growth hormone levels may be the most sensitive to radiation and may be the first to decline, but these levels are not routinely evaluated given the minimal clinical relevance of low growth hormone levels in the adult patient [59]. The same may also be true for prolactin, with levels sensitive to radiation but having minimal clinical impact [60]. One retrospective series looking at 385 patients who received fractionated radiation for pituitary adenomas from 1974 to 2003 treated to a median dose of 45 Gy found that approximately 20% of men with good hormone function prior to radiation had deficiencies at 5 years from treatment and 30% were deficient at 10 years from treatment [21]. A 20–30% occurrence of new hormone deficiencies at 10 years after fractionated radiotherapy has been described elsewhere [21, 35, 42, 43, 61, 62]. The results following radiosurgery appear similar. A cohort of 418 patients treated with GK with a median follow-up of 2.5 years found new onset pituitary hormone deficiency in approximately 25% of patients [22]. And similar rates have been shown elsewhere [7, 8, 31, 36, 37, 39, 40, 44, 51, 52]. The rates of hypopituitarism appear to increase as the time interval increases from radiotherapy, with rates of up to 80% at 1–1.5 decades out from treatment [35, 61]. Most of the available data is from less than 10 years of follow-up; the rate of hypopituitarism may continue to climb to levels of near 100%. These rates are summarized in Tables 33.1, 33.2, 33.3, and 33.4. Panhypopituitarism has been reported in 5–10% of patients at 5 years and also increases with time [27, 36, 37, 43, 44, 51]. Certain populations may be at higher risk of hypopituitarism following radiation therapy, including those with prior surgery and those with preexisting pituitary deficiencies [48, 59, 63].

It is for these reasons that all patients receiving peri-sellar radiation be informed of the high risk of iatrogenic hypopituitarism. With the pituitary adenomas in close proximity to the normal pituitary and hypothalamus by definition, preventing dose to the pituitary is typically unavoidable and, thus, hypopituitarism inevitable. An endocrinologist or a knowledgeable internist should follow these patients with neuroendocrine function surveillance starting from 6 to 12 months out from radiotherapy, so that hormone replacement therapy can be initiated when needed and prior to the manifestation of clinical symptoms of hormonal deficiency. They should remain on long-term follow-up, as hypopituitarism is a late effect of radiation and may take many years to manifest. Hypopituitarism and its sequelae can be treated very effectively with hormone replacement. When designing the radiation plan and defining targets, it is important to minimize the dose to the normal pituitary and the hypothalamus, which may reduce the risk of hypopituitarism [60, 64, 65].

Visual Pathway Injury

Side effects from pituitary irradiation other than hypopituitarism are less common. The optic pathway, particularly the optic chiasm and optic nerves, is a structure at risk in sellar irradiation with the potential for grave quality of life implications. A large series of 385 patients, described previously in the context of hypopituitarism, found a rate of optic neuropathy at 10 years to be <1% with fractionated radiation [21]. An older study of over 400 patients treated with fractionated radiation to 45–50 Gy found visual deterioration in 1.5% of patients at 20 years [66]. These rates are low because the radiation tolerance of the optic system is generally greater than the 45–54 Gy usually applied for pituitary tumors. The risk may be higher in the setting of preexisting visual deficits. Risk of toxicity to the optics appears to increase when delivering doses above 60 Gy for fractionated cases and above 12 Gy for radiosurgery cases [67, 68]. One series found zero cases of optic complications in 35 patients treated with radiosurgery in a single fraction if the dose to the optics was held to less than 8 Gy [69]. The therapeutic window is greater with conventional fractionation than with radiosurgery, so if a therapeutic dose is unable to be delivered to the target without exposing the normal tissues to levels of radiation above their tolerance, conventional fractionation is preferred. Damage to the optics is devastating to a patient's quality of life, so these constraints are often thought of as inviolate. A general approach of minimizing the radiation dose to the optics, keeping it as low as is reasonably achievable, is recommended.

Other Cranial Nerve Deficits

Damage to cranial nerves other than the optic nerve is also uncommon. A large review of 25 series with over 1600 patients identified only 21 patients with new neuropathies, and almost half were transient neuropathies [1]. Prior radiation therapy, however, may increase the risk of nerve damage [70]. One series examining radiosurgery for 62 patients found nonoptic cranial neuropathies in eight patients, three of which were transient. Two cases were in the setting of prior high-dose radiation exposure; the other cases occurred at doses >18 Gy [69]. Patients with prior irradiation or neuropathic comorbidities, such as diabetes, vascular disease, or baseline cranial nerve dysfunction, may represent a population at higher risk for nerve injury; for this group, one can consider fractionated radiation to decrease the risk of damage to nerves in or near the treatment field.

Secondary Tumors

Two large studies totaling almost 800 patients found the incidence of tumors caused by radiation therapy for pituitary adenomas to be 1.9% at 20 years [21, 66]. The secondary tumors identified were lymphomas, gliomas, meningiomas, or sarcomas. Limitations of these studies include the use of data spanning over several decades

and thus include older radiation therapy techniques. These older, less-conformal techniques exposed larger volumes of bystander tissue to higher doses of radiation. The imaging and localization techniques employed in modern radiation therapy minimize uncertainty in radiation delivery and result in smaller, more conformal treatment fields. Regardless, all patients with a reasonable life expectancy should be cautioned on the small but real late risk of developing a secondary neoplasm induced by prior radiation exposure.

Strokes

Patients with pituitary adenomas appear to be at increased risk for stroke, as high as a fourfold increase in risk compared to the general population [71, 72], but radiation after surgery does not appear to be associated with an increased risk of stroke compared to treatment with surgery alone [72, 73]. More extensive surgeries or greater doses of radiation may further increase the risk of stroke. Endocrine disturbances and associated cardiovascular sequelae in these pituitary adenoma patients may also be a contributing factor [71].

Conclusion

Radiation is effective for pituitary adenomas with local control rates of 90–100% across histologies but is not typically employed as a first-line therapy because of the high risk of secondary hypopituitarism. Biochemical complete response is achieved in approximately 50% of patients at 5 years; these rates are higher with the use of additional medical therapies. Biochemical response may take months to years to appreciate its full effect. Radiotherapy is a useful treatment for tumors that fail other modalities. There exist a variety of radiation delivery therapy systems that are effectively used. The techniques of target delineation and radiation delivery have improved over the last several decades, allowing for high treatment conformality with minimal exposure to bystander normal tissue that provides for a wider therapeutic window. Hypopituitarism is a common adverse effect from radiation therapy. Other adverse effects are much less common and will likely be recognized as increasingly rare as data matures from the era of current radiation therapy techniques.

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Cytotoxic Chemotherapy and Targeted Therapy for Aggressive Pituitary Tumors

34

Alissa A. Thomas and Camilo E. Fadul

Introduction

Pituitary tumors are usually benign entities that can be treated with surgery, radiation, and medical therapy, including dopamine agonists and hormonal therapy. Despite judicious implementation of these treatment modalities, a subset of pituitary tumors may become aggressive with local invasive recurrence or with metastases. Cytotoxic chemotherapy is not traditionally considered an effective therapeutic option because even when the tumor has an aggressive biologic behavior, the cancer cells are well differentiated and have a low proliferation rate. In 2006, however, our group and others reported on the response of aggressive pituitary tumors to temozolomide, an alkylating cytotoxic agent. Since then, chemotherapy has been used off-label in multiple cases, and although there are no controlled trials to date, the therapeutic benefit, as measured by response rate, has been consistent. Furthermore, as the cell-signaling mechanisms responsible for tumor growth are elucidated and in the advent of targeted therapies, we have an opportunity to improve the outcomes for patients diagnosed with aggressive pituitary tumors.

In this chapter we will discuss the medical oncologic management of aggressive pituitary adenomas and pituitary carcinomas. We will review the published experience using cytotoxic chemotherapy, anti-angiogenic therapy, and targeted therapy for pituitary tumors, and we will discuss biomarkers that are potentially predictive of response, keeping in mind two caveats. First, there are no controlled trials that evaluate the outcomes of these treatments, and, therefore, their effectiveness is based on anecdotal case studies. Second, the categorical designation of "aggressive

A.A. Thomas, MD
Department of Neurology, University of Vermont College of Medicine, Burlington, VT, USA

C.E. Fadul, MD, FAAN (✉)
Department of Neurology, University of Virginia, Charlottesville, VA, USA
e-mail: CEF3W@hscmail.mcc.virginia.edu

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_34

pituitary tumor" includes a heterogeneous group of diseases that, although histologically similar, may have very different mechanisms of tumorigenesis and therapeutic response.

The malignant behavior of pituitary tumors is determined by biologic characteristics as well as invasion into surrounding structures. Pituitary tumors constitute about 15% of all intracranial neoplasms [1], and 35–50% of these tumors are locally invasive [2]. Some invasive tumors are resistant to standard medical therapies, including dopaminergic agents and hormonal therapy. Others may recur after initial response to treatment. When the cellular proliferation rate exceeds 3%, these recurrent aggressive tumors are classified by the World Health Organization (WHO) as atypical pituitary adenomas. Though these neoplasms are locally invasive and histologically may differ from typical tumors, atypical pituitary adenomas rarely metastasize. It is estimated that 25–55% of pituitary adenomas are clinically aggressive, and display such features as invasion into surrounding tissue, as well as rapid growth, large size, and rapid recurrence [3]. After standard therapeutic options have been exhausted, patients who suffer from recurrence of these malignant tumors are presented with very limited options.

Pituitary carcinomas are a rare subgroup of pituitary tumors defined by the WHO as having systemic metastases or craniospinal dissemination. These aggressive cancers account for an estimated 0.2% of all pituitary tumors. Between 1961 and 2012 less than 150 cases were reported in the literature [4, 5]. From the histologic and endocrinologic perspectives, these tumors may be indistinct from benign pituitary tumors. Pituitary carcinomas most often secrete prolactin (36%) or adrenocorticotrophin (ACTH, 30%), while a smaller number are nonfunctional (23%) [5]. The most frequent sites of metastases are within the brain and spinal cord, but extracranial spreading of the neoplasm can also occur. There are no endocrinologic or pathologic characteristics known to predict which patients will develop metastases from a pituitary tumor. The molecular mechanisms that allow the tumor to metastasize also remain unknown. Although, in most patients, pituitary carcinomas behave aggressively with functional impairment leading to death, a few patients have reportedly lived for several years without medical treatment [2, 6]. In the majority of patients with pituitary carcinoma, the only treatment option is supportive care.

Pituitary tumors with certain histologic subtypes and biologic characteristics are associated with more malignant behavior. For example, prolactinomas are often more aggressive and less responsive to dopamine agonist therapy in men than women [3]. Another inherently aggressive pituitary neoplasm is the Crooke cell tumor, a corticotroph adenoma that undergoes massive accumulation of perinuclear cytokeratin in the presence of glucocorticoids [3]. In a study of 36 cases of this type of tumor, 60% of patients had recurrent disease with an average time to recurrence of 3.6 years [7]. Of the 25 patients who were followed for more than 1 year, two developed metastatic carcinoma. Silent corticotroph adenomas are even more aggressive than either their hormone-secreting counterparts (ACTH-secreting tumors) or other nonfunctioning adenomas. Though morphologically similar to ACTH-secreting tumors [3], they are characterized by higher rates of recurrence and more frequent invasion into the cavernous sinus [3]. Other pituitary tumors reported to

Table 34.1 Chemotherapy drugs that have been reported for the treatment of invasive pituitary tumors

Chemotherapy
5-fluorouracil with lomustine[a]
Gliadel wafers
Temozolomide[a]
Carboplatin
Paclitaxel
Etoposide
Capecitabine and temozolomide[a]

[a]Indicates that clinical or radiographic responses were reported

have an aggressive clinical course include gonadotropin-secreting pituitary adenomas, sparsely granulated somatotroph adenomas, densely granulated lactotroph adenomas, acidophil stem-cell adenomas, thyrotroph adenomas, plurihormonal adenomas, silent adenomas, and null cell adenomas [3]. These types of pituitary tumors should alert the clinician about a potentially more malignant behavior.

No standard-of-care recommendation exists for patients with aggressive pituitary tumors and carcinomas. Pituitary tumors that are invasive, recurrent, or metastatic pose a therapeutic challenge, as these neoplasms are often not manageable with local treatments such as surgery or radiation therapy. In most cases, dopamine agonists and hormonal therapies have limited benefit. Although the potential for systemic therapy with cytotoxic and targeted agents to improve outcomes for patients with malignant pituitary tumors is unknown, the reports to date suggest that these therapies could become an effective addition to the therapeutic armamentarium.

Cytotoxic Chemotherapy

Multiple cytotoxic chemotherapy agents have been used for the treatment of patients with recurrent aggressive pituitary tumors and pituitary carcinomas (Table 34.1). The benefit of chemotherapy in this patient population can be measured by response rate, as determined by tumor size in imaging studies, reduction in hormone concentration, progression-free survival, and overall survival. It is difficult to compare outcomes among studies because of the heterogeneity of the tumors treated and the variability in survival rates between locally invasive pituitary adenomas and pituitary carcinomas. As previously mentioned, some patients may experience prolonged survival without treatment. Of the aforementioned outcome measurements, radiographic response rate is the most consistently reported in studies using chemotherapy for malignant pituitary tumors.

Early publications on the use of chemotherapy for aggressive pituitary tumors were restricted to a few single case reports. The diversity of administered drugs limits the assessment of clinical utility [8]. The first series reported on seven patients with highly aggressive or malignant pituitary tumors who showed a disappointing response rate of only 14% after treatment with a combination of

5-fluorouracil (5-FU) and cyclo-hexyl-chloroethyl-nitrosourea (lomustine, CCNU) [9]. Three of these seven patients received single-agent carboplatin after progression with 5-FU/CCNU, but none responded on the basis of imaging assessment. In another trial, Gliadel wafers (1, 3-bis (2-chloroethyl)-1-nitrosourea [BCNU] and a biodegradable polyanhydride copolymer) were implanted postresection in nine patients with aggressive recurrent pituitary adenomas. Although potential benefits could not be determined from this single study, the patients tolerated the treatment without significant adverse reactions [10].

In 2006, we reported two cases of patients with pituitary carcinoma [11] who had remarkable responses on MRI to treatment with temozolomide. The first patient had a luteinizing-hormone-secreting pituitary adenoma with several local recurrences despite treatment with fractionated radiation and radiosurgery in addition to multiple surgical resections. About 8 years after his initial diagnosis, he was found to have multiple intradural and extramedullary lesions in the cervical and thoracic spinal cord. Biopsy of one of these lesions confirmed a typical pituitary tumor similar to the samples previously resected. Staging studies showed metastases in the ribs and right tibia, as well as growth of the original sellar tumor. He underwent radiation to the spinal lesions and received octreotide without effect. He was then enrolled in a Phase I study combining temozolomide and pegylated interferon. The interferon was stopped after 1 month due to Grade 4 fatigue. He continued temozolomide 200 mg/m^2/day on days 1–5 of 28-day cycles for 12 cycles. He tolerated the treatment well and had clinical improvement, as well as radiographic response (Fig. 34.1). Sixteen months after stopping chemotherapy, he remained asymptomatic. The second patient was a 26-year-old man with a prolactin-secreting pituitary adenoma who had progression with disseminated disease in the cervical and thoracic cord after treatment with dopamine agonists, surgery, and radiation therapy. He had previously received treatment for the metastatic disease, including bromocriptine, octreotide, carboplatin, paclitaxel, and etoposide, without response. Based on our experience with the prior case, the patient was treated with oral temozolomide 200 mg/m^2/day on days 1–5 of a 28-day cycle. He finished 10 of 12 planned cycles (stopped early due to fatigue), with improvement in symptoms, decreased prolactin concentration, and a partial radiographic response. Both patients had clinical and radiographic responses that were durable for more than 1 year after discontinuing the treatment, but both cases ultimately progressed without response after restarting temozolomide. Since then, several other reports have confirmed the sensitivity of aggressive pituitary tumors and pituitary carcinomas to temozolomide [11].

Temozolomide is an alkylating chemotherapy agent that works by methylating DNA at the O6 position of guanine (Fig. 34.2) leading to mispairing with thymine during the next cycle of DNA replication and ultimately results in non-cell-cycle-specific apoptosis. In 2005, the FDA approved temozolomide for newly diagnosed glioblastoma after a randomized trial demonstrated improvement in overall survival in patients treated with radiation and temozolomide as compared to patients treated with radiation therapy alone [12]. The effect was modest with a median overall survival of 14.6 months (compared with 12.1 months) and an increase in 2-year survival to 26.5% from 10.4% [12]. A retrospective analysis revealed that patients

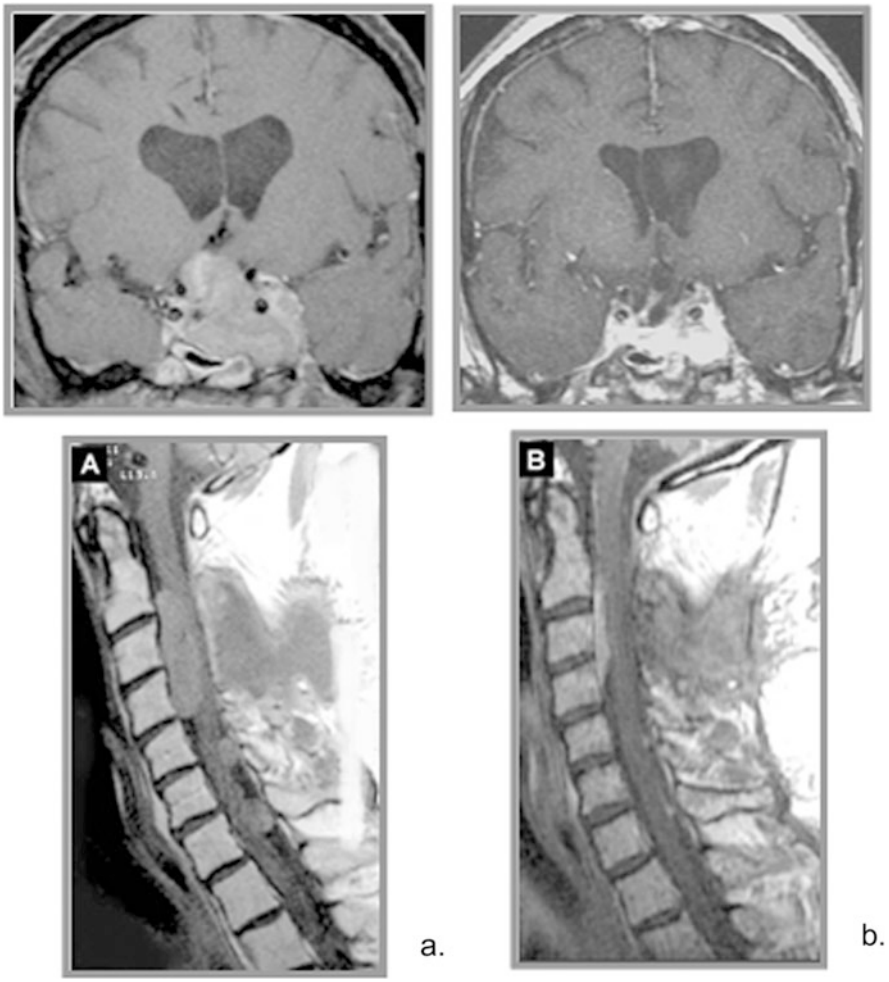

Fig. 34.1 A: Coronal contrast-enhanced T1-weighted MR image of the brain obtained before treatment, revealing an invasive pituitary mass with suprasellar extension. B: Sagittal contrast-enhanced T1-weighted MR image of the spine obtained before treatment, demonstrating three extramedullary masses, the largest at C2–4. C and D: Coronal (C)and sagittal (D) contrast-enhanced T1-weighted MR images showing decreases in the pituitary mass and spinal metastases, respectively, after 12 cycles of chemotherapy. (Reproduced with permission from: Fadul CE, Kominsky AL, Meyer LP, et al. Long-term response of pituitary carcinoma to temozolomide. Report of two cases. J Neurosurg. 2006;105(4):621–6.)

whose tumors harbored hypermethylation of the gene promoter of the DNA-repair enzyme O6-methylguanine-methyltransferase (MGMT) had a significantly better response to treatment; the median overall survival was 21.7 months, and 2-year survival rate was 46% [13]. MGMT repairs DNA by removing the methyl group from guanine, thereby undoing the damage caused by temozolomide. When the promoter region of MGMT is methylated, the gene is epigenetically silenced, and temozolomide has greater activity.

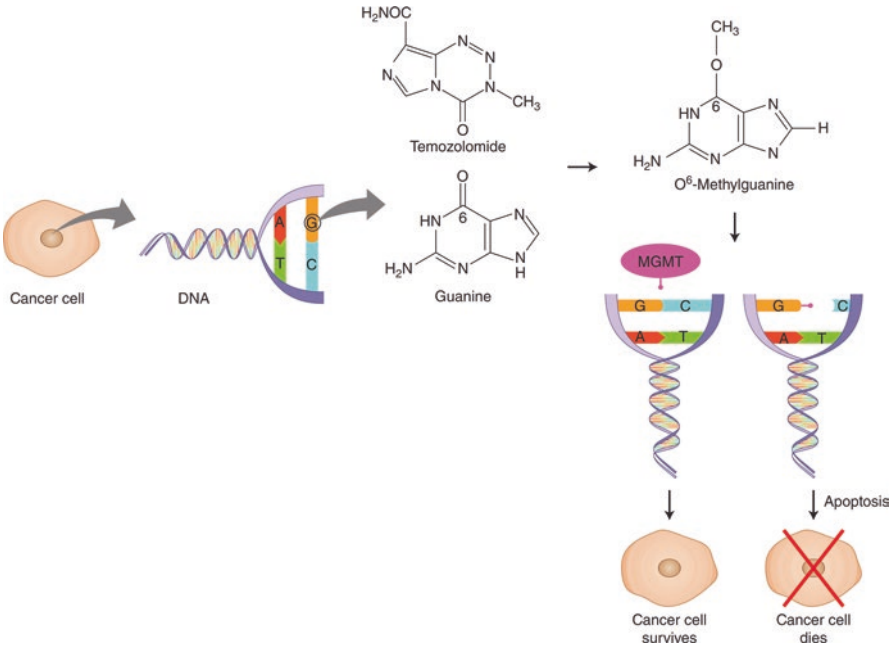

Fig. 34.2 Schematic representation of temozolomide mechanism of action. Temozolomide acts by adding a methyl group to the O6 position of guanine on the DNA of cancer cells. The O6-methylguanine is unable to pair with cytosine and the DNA cannot replicate, so the cell is forced to undergo apoptosis and die. MGMT is a DNA-repair enzyme that removes the methyl groups, repairing the damage done by temozolomide and allowing the cell to survive

The reports supporting the use of temozolomide in patients with aggressive pituitary tumors have been growing in the past decade [14, 15]. Overall, these studies suggest that the drug may have activity against a variety of subtypes of pituitary tumors, including Crooke's cell tumors [16], prolactinomas [17], and nonfunctioning pituitary adenomas [18], as well as tumors secreting luteinizing hormone (LH) as previously described [11]. Temozolomide may also be effective in treating extraneural metastases [19]. However, not all tumors are sensitive, as demonstrated by a case series of four patients with somatotropic pituitary adenomas that did not respond to temozolomide [20]. Therefore, in the absence of controlled trials, the challenge is to deepen our understanding of the mechanisms of cytotoxicity and resistance in order to determine which patients are more likely to benefit from temozolomide and what combinations of cytotoxic chemotherapy agents have the most favorable outcomes.

Since most reports include single cases or small series, meta-analysis of the cases is used to better assess the effectiveness of temozolomide in this disease. One meta-analysis included 46 patients, 30 with pituitary adenomas and 16 with carcinomas, who received treatment with temozolomide [21]. Clinical and radiographic responses occurred in 60% of the adenomas and 69% of the carcinomas. Another meta-analysis [4] of 21 additional patients from three studies [22–24] reported that seven patients (33%) with aggressive pituitary tumors responded to temozolomide and five more had stable disease, suggesting an overall disease control rate of 57%. The most recent

Table 34.2 Cases published of patients with aggressive pituitary adenoma or pituitary carcinoma treated with at least two cycles of temozolomide

		Response by MRI			Hormone response	
Type of pituitary tumor	*N*	CR + PR (%)	SD (%)	PD (%)	*N*	Decrease (%)
Aggressive invasive[a]	62	38 (61%)	6 (10%)	18 (29%)	13	11 (85%)
Carcinoma[b]	38	24 (63%)	4 (11%)	10 (26%)	14	11 (79%)
Aggressive/Carcinoma[c]	31	11 (35%)	14 (45%)	6 (19%)	21	15 (71%)
Total[d]	131	73 (56%)	24 (18%)	34 (26%)	48	37 (77%)

CR Complete Response, *PR* Partial Response, *PD* Progressive Disease
[a][15, 16, 20, 22–24, 26–28, 34, 41, 43–54]
[b][11, 14, 19, 22–24, 34, 36, 44, 49, 55–60]
[c]This reference includes six cases of pituitary carcinoma and 25 cases of locally aggressive pituitary tumor, but report does not discriminate response by type of tumor [25]
[d]Only included cases that received at least two cycles of temozolomide

meta-analysis reported an 80% response rate among 31 patients with aggressive pituitary tumors (six with carcinoma and 25 with adenoma) treated with temozolomide [25]. Of the 25 temozolomide responders, 13 had tumor growth after the temozolomide was discontinued. In our review of the published literature, 131 patients with aggressive pituitary adenoma or pituitary carcinoma have been treated with temozolomide for at least two cycles (Table 34.2). The radiographic response rate was 56% with an additional 18% of patients with stable disease, for a total of a 74% disease control rate. Among secretory tumors, 77% had a response as determined by a decrease in hormone secretion. Although the combination of these case reports and case series suggests that temozolomide may be an effective therapy for treatment-refractory pituitary adenoma and carcinoma, the optimal duration of therapy and the influence in progression-free and overall survival remain unanswered questions.

In most cases, progression has been observed after months to more than a year after stopping temozolomide [11, 26]. The mechanisms of resistance have not been elucidated, but it has been suggested that like in glioblastoma, temozolomide can cause secondary mutations. In our first two patients with pituitary carcinoma treated with temozolomide, both had recurrence more than 18 months after having completed 12 cycles of temozolomide. There was no response when the patients received temozolomide again. Another case report described a patient with an atypical aggressive pituitary adenoma that responded well to treatment with temozolomide, but then recurred after 6 months of stopping therapy [27]. A mutation in the mismatch repair gene MSH6, not present in the initial specimen, was found at recurrence.

Temozolomide has been combined with other cytotoxic chemotherapy for the treatment of aggressive pituitary tumors in an attempt to circumvent resistance. Four patients with aggressive ACTH-secreting pituitary tumors that progressed after surgeries, radiation, and hormonal therapy [28] were treated with a regimen of temozolomide (150 mg/m^2/day administered on days 10–14 of a 28-day cycle) and capecitabine (1000 mg BID on days 1–14) (CAPTEM). Of the four patients, two had radiographic complete responses, one had a 75% tumor regression, and the other had stable disease without progression after 4.5 years of follow-up. All tumors had low MGMT

expression by immunohistochemistry. Two other patients treated with CAPTEM have been reported, one with a corticotroph adenoma [29] and one with a prolactinoma associated with multiple endocrine neoplasia (MEN) [30]; both had a clinical and hormonal response to treatment [31]. The benefit of adding other chemotherapy agents to temozolomide in patients with aggressive pituitary tumors has not been established, but molecular profiling may provide the rationale for more effective combinations.

Similar to the experience in glioblastoma, patients with pituitary tumors tolerate treatment with temozolomide well. Grade 1 and 2 fatigue and thrombocytopenia are the most frequently reported side effects. Only one report of a severe temozolomide-related adverse event in a patient with a pituitary carcinoma has been published. A 58-year-old man with an ACTH-secreting pituitary carcinoma presented to the hospital with severe headache, blindness, and nuchal rigidity 27 days after starting temozolomide. He was found to have profound thrombocytopenia with multiple intraparenchymal cerebral hemorrhages from brain metastases. He died a few months later. This event highlights the potential life-threatening complications of temozolomide and the need for close monitoring when the disease and treatment combination have not been well characterized.

Biomarkers Predictive of Response

As with any other therapeutic decision, there is a need to identify patients with aggressive pituitary tumors who would benefit the most from temozolomide. The DNA-repair enzyme MGMT is a well-validated biomarker that predicts response to temozolomide and overall survival in patients with glioblastoma [13]. MGMT expression can be determined by a number of different assays, but there is no consensus on the measurement methodology that will provide the best correlation with response to this agent. Methylation assays, including methylation-specific polymerase chain reaction (PCR), real-time quantitative methylation-specific PCR, and methylation-specific multiplex ligation-dependent probe amplification, detect MGMT promoter methylation at CpG islands. Methylated MGMT represents the inactivated form of the enzyme, while unmethylated MGMT retains its enzymatic activity. MGMT protein expression can be determined by immunohistochemistry.

The correlation of MGMT methylation detected by PCR and protein expression by immunohistochemistry has been poor. One study of aggressive pituitary adenomas and carcinomas attempted to correlate MGMT protein expression with MGMT promoter methylation [32]. Among 14 carcinomas, 33% exhibited MGMT promoter methylation, while low MGMT protein expression was found in 50% by immunohistochemistry. Similarly, among the 12 aggressive adenomas, 42% had a methylated MGMT promoter region, while immunohistochemistry for MGMT was negative in 92% of the tumors. The lack of concordance between MGMT methylation and immunohistochemistry for protein expression is similar to that which has been reported with glioblastoma, where the methylation status is the predictor of response [33].

Most studies reporting on MGMT activity in pituitary tumors have relied on immunohistochemical assays [28, 34–37], with the suggestion that MGMT protein deficiency predicts response to temozolomide [35]. In the largest series to date, tissue

from 24 patients with aggressive pituitary tumors (16 aggressive adenomas and eight metastatic pituitary carcinomas) treated with temozolomide was retrospectively analyzed for hormone status, response to temozolomide, and MGMT protein expression by immunohistochemistry [34]. Of the 24 patients, 10 had a response to treatment (two radiographic complete responses, seven partial responses, and 1 hormonal response with 71% decrease in prolactin). Among the ten responders, median MGMT expression was 9% (range of 5–20%), compared with 93% in nonresponders (range 50–100%). A study of 197 pituitary adenomas revealed MGMT expression was low in the majority of tumors (86.3%) [38]. Although these studies suggest that aggressive pituitary adenomas with low MGMT protein expression by immunohistochemistry may respond to temozolomide, the glioblastoma literature suggests that the MGMT methylation status of the promoter may be a better predictive biomarker for response.

Loss of the DNA mismatch repair protein MSH6 has been implicated in the development of temozolomide resistance even when MGMT expression is low [27]. The presence of MSH6 by immunohistochemistry positively correlated with response to temozolomide in 13 cases of atypical pituitary adenomas and pituitary carcinomas. In another series, there was one case with absent MSH6 in which there was resistance to the drug, but several other cases also had rapid progression in spite of having expression by immunohistochemistry [34]. The small number of retrospective cases precludes any conclusions about its value as a biomarker of responsiveness to temozolomide.

Anti-angiogenic Therapy

Vascular endothelial growth factor (VEGF) is a pro-angiogenic cytokine that drives neovascularization in many cancers. Bevacizumab, a monoclonal antibody that targets VEGF, is FDA approved for the treatment of several solid tumors, including recurrent glioblastoma. VEGF has been reported to be present at high concentrations in 59% of pituitary adenomas [38]. The presence of VEGF and the invasive behavior of some pituitary adenomas provide rationale for the use of bevacizumab for the treatment of refractory disease. There has been one case report showing stabilization of an aggressive pituitary adenoma after bevacizumab treatment [39]. A 44-year-old man presented with an aggressive silent corticotroph cell pituitary adenoma, which was refractory to multiple treatments and progressed despite the use of temozolomide. Bevacizumab was initiated, and after 10 months of therapy the tumor remained stable. Bevacizumab was continued for another 16 months with ongoing disease control for the duration of follow-up (26 months). Though this is only a single case, the successful long-term disease control is encouraging. It is possible that the combination of temozolomide and bevacizumab could be an effective option for refractory disease.

Targeted Therapy

There has been limited experience combining temozolomide with the somatostatin analog, pasireotide. The first report described a patient with an ACTH-secreting pituitary carcinoma with widespread intracranial, spinal, and systemic metastases

despite repeated surgical treatment, bilateral adrenalectomy, medical treatment, and chemotherapy [40]. The patient received temozolomide and pasireotide combination therapy for 12 months. The combination was well tolerated, and the patient had improvement in symptoms and reduction of ACTH levels. Pasireotide was continued for 9 months as monotherapy after temozolomide was discontinued. A case series of five patients with aggressive pituitary adenomas treated with temozolomide included two patients with secreting tumors who received both temozolomide and pasireotide [41]. One of the two patients responded to combination therapy with a decrease in both cortisol concentration and tumor volume.

Preclinical studies suggest that aggressive pituitary adenomas may be sensitive to treatment with PIK3/mTOR inhibitors and that these drugs may augment the response to temozolomide [42]. Hyperactivity of the PIK3/Akt/mTOR pathway is thought to contribute to chemotherapy resistance. In pituitary adenoma cell lines, XL756, a novel dual PIK3/mTOR inhibitor, given in combination with temozolomide inhibited adenoma cell growth and induced apoptosis to a significantly greater extent than temozolomide alone. The combination of XL756 and temozolomide synergistically inhibited tumor growth and resulted in decreased serum growth hormone and prolactin concentrations in a murine xenograft model [42]. This suggests that dual inhibition of PIK3 and mTOR may enhance alkylating agent-mediated cytotoxicity in pituitary tumors, but there is no clinical experience with this combination.

One patient with an ACTH pituitary carcinoma resistant to temozolomide has been treated with everolimus (an mTOR inhibitor) in combination with octreotide. Treatment failed to control tumor growth and hormone secretion, with the lack of response thought to be explained by the weak mTOR activation in ACTH tumors. It must be determined whether mTOR inhibition is a more prominent mechanism of tumorigenesis in other types of aggressive pituitary tumors and if response to inhibition will correlate with its activation.

Indications for Chemotherapy

Invasive pituitary adenomas and pituitary carcinomas are uncommon pituitary neoplasms with high rates of recurrence and responsible for significant morbidity and mortality. In these aggressive tumors, it may be impossible to achieve local control with radiation therapy or surgery due to infiltration into surrounding tissues or metastatic dissemination. In the absence of a clear hormonal target with established endocrine therapy, temozolomide may be considered for the treatment of these tumors. Controlled prospective data is lacking to support the use of temozolomide for this indication, but several case reports and case series demonstrate both safety and clinical, hormonal, and imaging efficacy, sometimes with prolonged and durable responses. Temozolomide is most likely to be effective when the tumor has a methylated MGMT promoter. Although the adverse side effects of temozolomide are usually mild to moderate, close monitoring is still imperative.

The Future of Chemotherapy for Pituitary Tumors

To better understand the indications for cytotoxic chemotherapy, controlled prospective data is needed with attention to the subtypes of pituitary cancers that most often develop an invasive phenotype and the biomarkers that may be predictive of response. Because these tumors are uncommon, it may be necessary to establish a referral center of excellence or involve cooperative groups in order to develop clinical trials that assess the efficacy of chemotherapy for this disease.

Case reports and case series of temozolomide have been encouraging, but there are many unanswered questions about the use of this drug for invasive pituitary cancers. In most case reports, patients received a standard dose of temozolomide [12], but it is unclear whether this is the optimal dosing schedule for pituitary tumors or if an alternative schedule such as continuous daily dosing or dose-dense treatment may be better. The duration of therapy is also unknown. In glioblastoma, 6 months of adjuvant temozolomide is recommended, but in practice temozolomide may be continued for 12, 18, or 24 cycles or longer. In several reports patients who initially had a response to temozolomide had recurrent disease after the temozolomide was stopped [11, 25]. A prospective trial could better establish the duration of treatment as well as the duration of response.

Combinations of temozolomide with anti-angiogenic therapy, targeted therapy (such as PIK3/mTOR inhibitors), and hormonal therapy need to be studied to determine the safety and clinical efficacy in pituitary tumors. We had observed that after an initial response to temozolomide, recurrent pituitary carcinoma may be resistant to additional treatment with temozolomide [11]. Patients with relapsed pituitary carcinoma who remain fit enough for therapy are rare, so designing clinical trials for this small population of patients is challenging, but this may be a population that benefits from combination therapy or from anti-angiogenic therapy. Invasive pituitary tumors are known to express VEGF, but there is only one case report of treating a patient with bevacizumab [39]. Larger studies may be able to confirm therapeutic benefit.

Some studies have started to elucidate the genetic contributors of invasiveness in pituitary cancers, but more data is needed to understand the pathways and mutations that drive tumor growth and invasion. Pituitary tumors are a heterogeneous group of tumors with different cells of origin and variable hormonal secretory status. With histologic diagnostic tools, it is not possible to predict which of these tumors are likely to become invasive or refractory to standard treatments. Molecular profiling and genotyping may be able to identify drivers of invasiveness and help to predict the tumors likely to transform to a malignant phenotype. With increased understanding of the molecular biology of pituitary cancers, we may be able to identify therapeutic targets.

Conclusions

Invasive pituitary adenomas and pituitary carcinomas are rare tumors that are often resistant to radiation and hormonal therapy and are surgically unresectable. Early clinical experience suggests that a majority of these tumors may respond to

chemotherapy with temozolomide. Limited molecular data points to some oncogenic pathways that may provide other targets for treatment. Though challenging to design, clinical trials are needed to optimize treatment in a way that can predictably improve patient outcomes.

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Quality of Life in Patients with Pituitary Adenomas

35

Douglas A. Hardesty and Andrew S. Little

Abbreviations

AcroQoL	Acromegaly Quality of Life Questionnaire
ASBQ	Anterior Skull Base Questionnaire
ASK Nasal-9	Anterior Skull Base Nasal Inventory-9
ASK Nasal-12	Anterior Skull Base Nasal Inventory-12
CushingQoL	Cushing Quality of Life Survey
HRQoL	Health-related quality of life
KPS	Karnofsky Performance Scale
QOL	Quality of life
SF-12	12-Item Short Form Health Survey
SF-36	36-Item Short Form Health Survey
SNOT-22	Sino-Nasal Outcome Test

Introduction to Quality of Life

Quality of life (QOL) is defined as the patient's perception of his or her general well-being. When QOL is considered within the context of medicine, the term *health-related QOL* (HRQoL) is used to indicate the influence of disease burden on patients. At its most expansive, it is a multidimensional concept that includes the patient's perception of his or her physical, social, emotional, and functional well-being. Assessment of QOL often involves inquiries into pain, daily activities, relationships with family, and psychosocial health. QOL is necessarily subjective; two

D.A. Hardesty, MD • A.S. Little, MD (✉)
Department of Neurosurgery, Barrow Neurological Institute,
St. Joseph's Hospital and Medical Center, 350 W. Thomas Rd., Phoenix, AZ, USA
e-mail: Neuropub@dignityhealth.org

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_35

patients with the same disease and the same morbidities may experience QOL differently, depending on their individual personal expectations and experience. QOL is not static and may improve or decline with or without accompanying changes in the individual's objective health status. The study of HRQoL in specific disease states has expanded dramatically in the last two decades as organized medicine, third-party payers, and patients have focused more on long-term outcomes and value-based reimbursement. The concept of QOL is especially important in patients with pituitary tumors because the overwhelming majority of these patients will not die from their disease. Thus, objective outcome measures, such as mortality, are less relevant. Instead, maximizing the QOL of patients during their chronic disease process becomes the primary goal of treatment. Since QOL end points capture the patient's perspective, they complement objective end points that are traditionally reported in surgical series. We have found that QOL data are particularly useful for preoperative patient counseling and management of patients' expectations. In this chapter, we review the objective scales designed to capture QOL in pituitary patients as well as the major factors that positively and negatively affect QOL in patients with both surgical and nonsurgical management of their pituitary tumors. Lastly, we examine unique QOL dilemmas associated with functional pituitary adenomas.

Quality of Life Scales Used in Transsphenoidal Surgery and Pituitary Tumors

Numerous scales have been developed to measure HRQoL. They can be broadly grouped into multidimensional scales (those that seek to measure several domains of a patient's well-being) and unidimensional scales (those that focus on one domain of recovery). Many of these scales are multidimensional and universal, with applicability to a wide variety of disease processes. These broad scales allow for a sampling of QOL-related items, but they do not necessarily adequately capture subtle QOL alterations in specific disease states. Therefore, most specialties within medicine have crafted their own site- and disease-specific QOL measurement tools to better capture common complications and morbidities.

In general, QOL metrics are self-reported by the patient. Numerous studies have shown poor correlation between physician assessment of patient QOL and the patient's self-reported QOL. Therefore, physician interpretation of patient QOL should be used sparingly and only when patients and their caregivers are not able to complete QOL metrics themselves.

Scales used to assess HRQoL should meet basic psychometric parameters. They should be validated in a way that demonstrates that the scale is reliable, reproducible, and sensitive to clinical change, and that its content is relevant to the population being studied. One challenge of studying QOL in pituitary patients is that very few scales have been developed specifically for this population. In fact, many of the scales that are applied to pituitary patients have been validated in other populations, which raises questions about their validity in pituitary patients. When selecting the

Table 35.1 Quality-of-life instruments used in pituitary research

QOL instrument	Assessment goal	Characteristics	Validated in pituitary patients
Karnofsky Performance Scale	Performance status in oncology patients	Unidimensional	No
SF-12 or SF-36	Global functional status	Multidimensional, generic	No
ASK Nasal-9 or ASK Nasal-12	Sinonasal function after transsphenoidal surgery	Site-specific	Yes
Sino-Nasal Outcome Test (SNOT-20 or SNOT-22)	Rhinosinusitis symptoms and impact on QOL	Disease-specific	No
Anterior Skull Base Questionnaire	Anterior fossa symptoms after open or endoscopic skull base surgery	Site-specific	Yes
CushingQoL	QOL related to hypercortisolemia	Disease-specific	Yes
AcroQoL	QOL related to excessive growth hormone	Disease-specific	Yes

Abbreviations: *AcroQoL* Acromegaly Quality of Life Questionnaire, *ASK Nasal-9* Anterior Skull Base Nasal Inventory-9, *ASK Nasal-12* Anterior Skull Base Nasal Inventory-12, *QOL* quality of life, *SF-12* 12-Item Short Form Health Survey, *SF-36* 36-Item Short Form Health Survey

appropriate scale to use, researchers should consider which end points they are trying to measure. Each QOL instrument has strengths and limitations that will have an impact on the results. Below, we review the most common QOL instruments used with pituitary patients (Table 35.1).

General HRQoL Scales

Karnofsky Performance Scale

The Karnofsky Performance Scale (KPS) is one of the most widely used metrics within neurological surgery, especially neurosurgical oncology. Originally devised in the 1940s by Karnofsky and Burchenal, it was rigorously validated in the 1980s in oncology patients [1]. However, it is a physician-determined value and is only a proxy for patient-centric QOL. The KPS is a gross unidimensional measure of patient functional status on a scale from 100 (fully functional; no morbidity) to zero (death), and it focuses on the ability of patients to perform their own activities of daily living. Broadly, patients can be classified by their KPS scores into three groups: 0–40 (no independence; requiring institutional care), 50–70 (some functional independence; variable supportive care needs but unable to work), and 80–100 (able to work and perform normal daily functions). Our experience suggests that KPS is not sensitive for pituitary patients, because most pituitary patients are able to carry out activities of daily living and therefore score in the highest KPS range.

12-Item Short Form Health Survey and 36-Item Short Form Health Survey

The 36-Item Short Form Health Survey (SF-36) and the 12-Item Short Form Health Survey (SF-12) derived from it are patient-reported QOL scales that have been broadly applied to many disease states [2–4]. Each survey covers eight domains of physical and mental well-being; the SF-12 contains 12 items derived from the SF-36 to retain most of the relevant information. Each metric is scaled to a numeric score from 0 (worst) to 100 (best). These scales are superior to KPS as a generic measure of patient QOL, because they are both multidimensional and self-reported; however, their acquisition and scoring require more effort. The weakness of these scales with respect to transsphenoidal surgery is that their content has not been validated for this patient population and thus they do not capture the subtle concerns of patients with pituitary tumors. However, these scales may be valuable in assessing overall HRQoL, and they have been applied extensively to pituitary patients [5].

Site- and Disease-Specific QOL Scales

Anterior Skull Base Questionnaire

The Anterior Skull Base Questionnaire (ASBQ) is the most widely published and utilized site-specific QOL measurement for anterior skull base surgery, including pituitary tumors [6, 7]. The ASBQ has been used both for patients undergoing endoscopic and microscopic resection of pituitary tumors and for patients undergoing open transcranial approaches for other benign and malignant lesions. This self-reported scale encompasses 35 questions within six domains; each question is equally weighted and scored from 1 to 5, so that possible results vary between a score of 35 (worst) and a score of 175 (best). The ASBQ contains general QOL assessments of pain, mood, and energy, as well as site-specific assessments of taste, smell, sinonasal function, and visual function. The drawback of this scale in pituitary surgery is that the content was not designed to assess patients with endocrine-active tumors. The ASBQ was originally designed to assess patients who underwent open skull base approaches and was only recently adapted to those undergoing fully endonasal approaches [8, 9].

Anterior Skull Base Nasal Inventory

The Anterior Skull Base Nasal Inventory (ASK Nasal) is a unidimensional and site-specific self-reported assessment of sinonasal symptoms (e.g., pain, crusting, and ease of breathing) after endonasal surgery. Unlike the ASBQ or the SF-12 or SF-36, a higher score in either ASK Nasal metric portends a worse QOL for the patient. The original ASK Nasal-9 is scaled on the basis of symptom frequency, with each of nine questions scored from 1 (never experiences) to 5 (constantly experiences). The ASK Nasal-9 metric has been validated in endoscopic and microscopic surgical patients undergoing pituitary adenoma resection [10]. More recently, the ASK Nasal-12 was published by the same authors as a refined three-question expansion of the original scale [11]. The ASK Nasal-12 is scored on a six-point Likert system,

ranging from 0 (no problem to patient) to 5 (severe problem). This differs from the ASK Nasal-9 in that the ASK Nasal-12 rates symptoms by their severity rather than their frequency. Furthermore, the authors asked patients to rate the top five symptoms that were most important to them, regardless of the score they assigned that symptom. These symptoms included pain and smell, and nasal obstruction symptoms; however, these symptom scores are not given extra weight in the ASK Nasal-12 scoring system. The purpose of this scale is to assess sinonasal function and recovery after transsphenoidal surgery. To date, this scale is the only one specifically validated for endonasal surgery. It is meant to complement other multidimensional tools used to study pituitary QOL.

Sino-Nasal Outcome Test

The Sino-Nasal Outcome Test (SNOT-22; originally SNOT-20) is a disease-specific self-reported assessment of sinonasal symptoms, originally designed to monitor clinical response to rhinosinusitis treatment [12, 13]. Symptoms are scored from 0 (no problem) to 5 (as bad as possible), on the basis of a patient-based combination of frequency and severity. As with the scores on the ASK Nasal inventories, worse symptoms result in a higher score. The SNOT scales have been used in numerous studies assessing sinonasal-related QOL in patients undergoing transsphenoidal surgery. However, our work suggests that not all items on the SNOT scales are important to transsphenoidal surgery patients. Nevertheless, it is a widely used and validated metric for sinus surgery, and it is frequently used in neurosurgical endonasal QOL studies.

Acromegaly Quality of Life Questionnaire

The Acromegaly Quality of Life Questionnaire (AcroQoL) is a disease-specific, self-reported, 22-item Likert-scale assessment of QOL symptoms in acromegaly based on endocrinologist and patient interviews [14]. Scores range from 22 (worst possible QOL) to 110 (best QOL). Patients with growth hormone-producing tumors have unique symptoms compared to those of patients with other functional and nonfunctional pituitary adenomas. AcroQoL samples these by questioning in domains such as perceived body image, socialization, and sexual function. The AcroQoL has been translated into multiple languages and validated in numerous studies [15, 16]. No items on the AcroQoL are related specifically to perioperative morbidity; the instrument can be used with both surgical and nonsurgical patients.

Cushing Quality of Life Survey

As with acromegaly, adrenocorticotropic hormone-producing pituitary tumors that lead to Cushing disease result in unique QOL concerns compared to those of patients with nonfunctional adenomas in the domains of body image, fatigue, and depression. Therefore, the Cushing QOL survey (CushingQoL) survey was developed for use in this population by patient interview to better assess QOL items not directly addressed in more generic QOL instruments [17]. The 12-item Likert-scale CushingQoL assesses symptoms during the 4 weeks prior to the assessment, with scores from 12 (worst QOL) to 60 (best QOL). Items specific to hypercortisolism

(e.g., "I bruise easily") are included, as are more generic mood items (e.g., "I'm worried about my health in the future"). The scale has been well validated and was used recently in a multicenter pasireotide study [18]. Like the AcroQoL, the CushingQoL contains no items specifically related to perioperative morbidity. The CushingQoL has been mapped to more generic QOL metrics such as the SF-36, allowing for the extrapolation of these values from the patient's CushingQoL score, even if the generic measure has not been obtained [19].

Factors Affecting QOL in Patients with Pituitary Tumors

QOL after transsphenoidal surgery is influenced by several factors, including the morbidity of the surgical approach and complications, disease status (remission vs. persistent disease), and endocrine function. Numerous authors have used the scales introduced in the preceding section to focus on various factors that influence the QOL of patients with pituitary tumors. Some factors that affect QOL are not modifiable by the patient or surgeon but are nevertheless important during preoperative counseling. Other factors affecting QOL are under the control of the patient or surgeon, and these areas are of considerable research interest in order to maximize patient QOL in the future.

Nonsurgical Factors

Hypopituitarism

Complete panhypopituitarism is a rare presurgical finding in patients with nonfunctional pituitary adenomas. More commonly, patients with adenomas may present with mild gland dysfunction in one hormonal axis. Postoperatively, panhypopituitarism is frequent in patients with nonadenoma sellar tumors, such as craniopharyngioma, but can also be seen, although rarely, in patients with adenomas. Recently, a 14% rate of new endocrinological deficit (one or more axes) was reported after pituitary adenoma surgery [20]. The loss of pituitary gland function must be identified so that hormones can be appropriately supplemented. Not surprisingly, untreated or undertreated hypopituitarism has a negative effect on patient QOL, whereas treatment improves QOL as assessed by generic patient-reported QOL measures [21, 22].

Morbidity and Efficacy of Medical Therapy

Not all functional pituitary adenomas require surgical removal; pharmacological therapy is also a common treatment for acromegaly and prolactinoma. Recent advances have also led to medical therapies for patients with Cushing disease. However, these medications may cause adverse reactions, problems with patient compliance, and drug-to-drug interactions that can negatively affect patient QOL. Despite improved biochemical disease control, the interplay of these factors can impact QOL. The medical treatment of Cushing disease with pasireotide has been shown in a randomized, blinded, dose-escalation trial to improve patient QOL as

measured by the CushingQoL metric [23]. The most significant improvements were found in those patients who achieved biochemical remission. Despite adequate treatment, patients with Cushing disease can have persistent QOL concerns [24]. However, the medical treatment of Cushing disease remains in its relative infancy, and further studies should better delineate the relative QOL improvements in medical versus surgical treatment paradigms.

In comparison, the medical treatment of acromegaly is well established and the QOL literature is more robust. Studies have shown improved QOL after treatment with formulations of octreotide and pegvisomant. Over a 4-year period, treatment with long-acting depot octreotide led to improved disease-specific QOL as measured by the AcroQoL; those patients whose QOL was the most improved also achieved biochemical remission or at least improvement in insulin-like growth factor 1 [25]. A 1-year follow-up observational study in German patients taking pegvisomant showed significant improvements in overall QOL, soft tissue swelling, and other factors [26]. Subjective symptoms that did not differ significantly after 1 year of treatment included headache, fatigue, and joint pain. Not surprisingly, the use of multiple simultaneous medications for acromegaly is associated with worsened QOL, likely due to a more aggressive disease process as well as to patient inconvenience and subjective dissatisfaction with having to take multiple medications [27].

Surgical Factors

Expected Perioperative Quality of Life Alterations

Surgery is invasive and associated with anxiety, pain, financial burden, and time away from family and work for the patient. Even with excellent surgical and perioperative care, patients undergoing removal of a pituitary adenoma will have a temporary decrease in QOL during the perioperative period. Sinonasal morbidity as a consequence of the transsphenoidal approach is a primary factor affecting QOL. Patients complain of nasal obstruction and congestion, anosmia, headache, and epistaxis. As noted on office endoscopy, common signs after transsphenoidal surgery include septal perforation, nasal crusting, and synechia (Fig. 35.1).

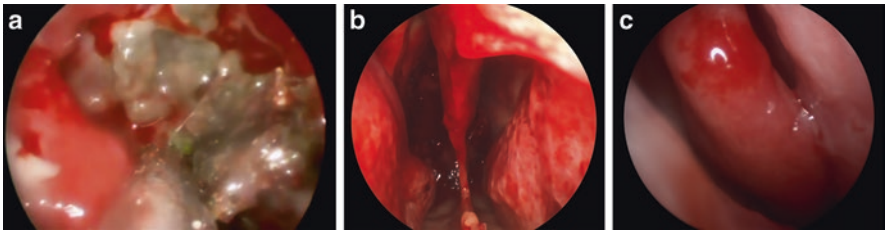

Fig. 35.1 Common nasal endoscopy findings after transsphenoidal surgery include (**a**) crusting, (**b**) septal perforation, and (**c**) synechia. These anatomical changes may diminish patient sinonasal quality of life (Used with permission from Barrow Neurological Institute, Phoenix, Arizona)

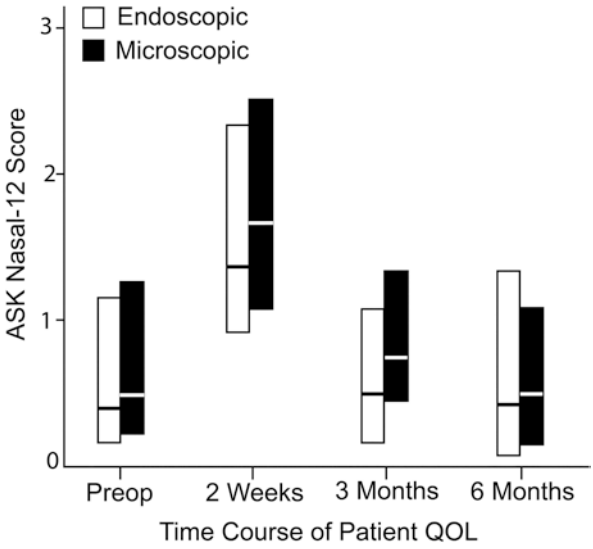

Fig. 35.2 Time course of patient-reported sinonasal quality of life (QOL) after endoscopic and microscopic transsphenoidal surgery. *ASK Nasal-12* Anterior Skull Base Nasal Inventory-12, *Preop* preoperatively (From Little et al. [31]. Used with permission from *Journal of Neurosurgery*)

Several authors have recently analyzed QOL after pituitary adenoma resection using multiple metrics [9, 28, 29]. Sinonasal-related QOL worsened after surgery as measured by SNOT-22 and ASK Nasal-12 but returned to baseline values by 6 weeks to 3 months postoperatively and subsequently improved beyond preoperative scores for most patients at 1 year after surgery (Fig. 35.2). Previously, our group [28] at Barrow Neurological Institute, Phoenix, Arizona, identified factors associated with worse short-term sinonasal morbidity, including advancing age, general HRQoL, sinusitis, and the use of nasal splits and absorbable nasal packing. Site-specific QOL, as measured by the ASBQ by McCoul et al. [8], also reaches a nadir several weeks after surgery but improves significantly in all domains after 6 weeks postoperatively. These data are similar to previously published results on mixed-pathology endonasal approaches, such as by Balaker et al. [30] at the University of California, Los Angeles, who found that significantly depressed QOL was related to sinonasal symptoms (as measured by SNOT-20), with normalization to preoperative values approximately 6 months after surgery. The endoscopic endonasal surgical approach described by Balaker et al. is more extensive with regard to maxillary antrostomies and turbinate resection than that described by other groups, which may explain the longer postoperative time course to resolution of sinonasal symptoms; Thompson et al. [29] published a follow-up study demonstrating improved QOL metrics with reduced soft tissue manipulation.

Endoscopic Versus Microscopic Transsphenoidal Surgical Approach

Microscopic transsphenoidal surgery for the removal of pituitary adenomas has been the standard of care for decades, but the advent of modern endonasal endoscopy in the last 20 years has made for surgical equipoise. At present, either surgical technique can produce excellent outcomes in the hands of an experienced surgeon

and team. Numerous centers have investigated whether the endoscopic endonasal transsphenoidal approach or the microscopic endonasal or sublabial transsphenoidal approaches produce superior QOL results. Little et al. [31] conducted a prospective multicenter cohort study assessing sinonasal morbidity and site-specific QOL in 218 patients undergoing either a binostril endoscopic resection or a uninostril microscopic resection. The ASK Nasal-12 was the primary metric, and results were equivocal overall between the two surgical approaches. At 3 months postoperatively, patients undergoing endoscopic endonasal approaches had site-specific QOL that was statistically superior to that of patients undergoing the microscopic approach, but this finding was not statistically significant at any other time point before or after. In contrast, Hong et al. [32] found slightly superior results with the endonasal microscopic approach over the endoscopic endonasal approach using the same ASK nasal inventory metric in their retrospective cohort series at 1 and 3 months postoperatively. They also examined postoperative olfactory-related QOL and found no difference between the two approaches. The surgical techniques between the Little and Hong groups varied slightly, which may explain the small differences found. At present, there is insufficient evidence to suggest that one surgical approach produces superior site-specific or generalized QOL results over the other in patients with pituitary adenomas who undergo transsphenoidal resection.

Nasoseptal Flaps

Vascularized pedicled nasoseptal mucosal flaps have drastically reduced the rate of cerebrospinal fluid leak after endoscopic endonasal transsphenoidal surgery [33]. However, the harvesting of a nasoseptal flap disrupts the normal nasal architecture and can lead to temporary increased site-specific morbidity and thus to decreased patient QOL (Fig. 35.3). Multiple groups have demonstrated that patients undergoing a standard vascularized nasoseptal mucosal flap repair have temporary worsening of olfaction, headache, and nasal crusting scores using QOL metrics such as SNOT-22 [34–36]. However, these effects appear temporary, and long-term QOL

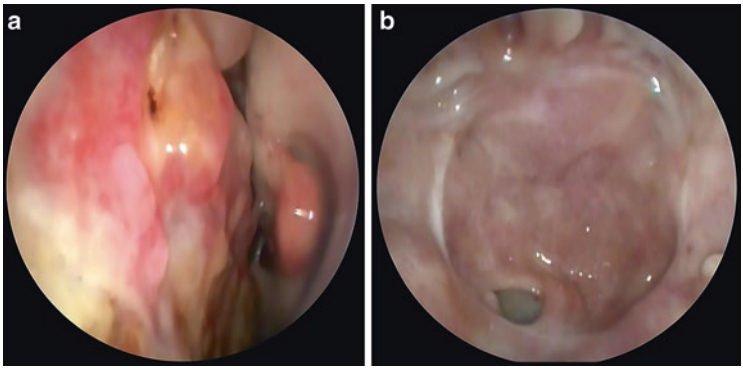

Fig. 35.3 Postoperative healing of a nasoseptal flap (**a**) at 3 weeks after surgery and (**b**) at 1 year after surgery (Photographs courtesy of Dr. Ryan Rehl. Used with permission from Barrow Neurological Institute, Phoenix, Arizona)

studies have shown little or no difference between both site-specific and overall QOL scores in patients undergoing nasoseptal flap reconstruction compared with QOL scores of patients undergoing other approaches [9, 34, 36, 37]. Furthermore, use of a nasoseptal flap may correspond with a more complex resection that requires longer and more extensive sinonasal manipulation, which confounds the analysis of the influence of the nasoseptal flap. In summary, the nasoseptal flap, when required, is well tolerated with regard to long-term patient QOL. However, the temporary worsening of site-specific QOL symptoms leads us to harvest the nasoseptal flap only when necessary.

Middle Turbinate Resection

In the endoscopic endonasal approach, resection of the middle turbinate allows for greater surgical exposure and can reduce "sword-fighting" between operators. However, like nasoseptal flaps, disruption of the normal sinonasal architecture may reduce site-specific patient QOL. The exact effects of middle turbinate resection during functional endoscopic sinus surgery have been debated in the otolaryngology literature [38]. In endoscopic surgery for pituitary adenoma, Thompson et al. [29] found decreased site-specific QOL as measured by SNOT-20 in patients who did and did not undergo middle turbinate resection. These authors also compared patients who underwent a less invasive, minimalist approach to historical controls who underwent more extensive routine turbinate resections, maxillary antrostomies, and sinonasal flaps. Not surprisingly, patients who underwent less sinonasal tissue resection and manipulation had better sinonasal QOL after surgery. However, these retrospective series may be limited by bias, in that more complex cases or patients with less favorable sinonasal anatomy may undergo more extensive turbinate resection and sinonasal tissue manipulation. Just as we do not routinely harvest nasoseptal flaps unless it is necessary, we also recommend preservation of the middle turbinate whenever possible to maximize patient QOL. However, when resection of the middle turbinate is indicated, it can improve surgical freedom; it is also fairly well tolerated, despite short-term decreases in site-specific QOL.

Olfaction

The sense of smell (i.e., olfaction) is crucial to taste and the enjoyment of food. Olfaction also allows the detection of, and the subsequent avoidance of, noxious hazards. Postoperative disturbances in olfaction or the total loss of olfaction after transsphenoidal surgery is associated with reduced QOL. Wang et al. [39] found objective olfaction assessments to be decreased as long as 4 months postoperatively after a microscopic transsphenoidal approach and identified a small proportion of patients (7.5% [4/53]) with permanent objective alterations in olfaction. A concurrent subjective decrease in site-specific and general QOL (as measured by SNOT-22 and SF-36) was also noted 1 week postoperatively, but these values normalized by 4 months. Hart et al. [40] also identified a transient worsening of olfaction, as measured by the University of Pennsylvania Smell Identification Test, at 1 month postoperatively in patients treated using purely endoscopic techniques, but these scores normalized to preoperative scores after 3 months. Worse olfaction

outcomes have been reported with the microscopic approach compared to the endoscopic transsphenoidal approach, with nasal synechia correlating with olfactory disturbances [41].

Complications

Postoperative surgical complications can lead to serious temporary or permanent reductions in patient QOL. However, the impact of certain complications on QOL outcomes has not yet been studied in depth. Fortunately, serious complications of either microscopic or endoscopic transsphenoidal approaches are relatively rare. Two large series that examined predictors of QOL in patients with pituitary adenomas either did not include surgical complications, such as cerebrospinal fluid leak, epistaxis, carotid artery injury, and cranial neuropathy, or attempted to examine these variables but did not observe any such events [9, 28]. When appropriately repaired, intraoperative cerebrospinal fluid leak was not associated with reduced QOL, as reported by McCoul et al. [9]. However, these authors did not observe any late cerebrospinal fluid leaks after surgery to analyze for QOL effects. The relative rarity of specific complications requires large multicenter QOL studies to examine related site- and disease-specific QOL metrics.

Specific QOL Concerns in Patients with Functional Pituitary Adenomas

Functional pituitary adenomas present unique QOL concerns because of the pervasive biochemical effects of hypersecretion. Thus, specific QOL metrics have been developed for patients with Cushing disease and acromegaly. No specific QOL studies have been performed on patients with tumors producing thyroid-stimulating hormone, likely because of their rarity.

Hypercortisolemia from Cushing disease leads to a familiar constellation of signs and symptoms (e.g., weight gain, fragile skin, mood alterations, and metabolic derangements). These and numerous other factors have been studied in relation to patient QOL. Most studies have demonstrated improved QOL in patients who achieve biochemical remission of disease [42, 43]. A myriad of other disease-related sequelae (e.g., depression, neurocognitive dysfunction, negative body image, and negative illness perceptions) is also associated with negative QOL in patients with Cushing disease who do or do not experience biochemical remission [24, 42, 44–47].

Elevated growth hormone levels in patients with acromegaly produce metabolic derangements and alterations in facial appearance, hand dexterity, and mood. Numerous studies have shown that biochemical control of growth hormone levels is associated with improved QOL [25, 48–50]. However, despite disease control with surgery or medical therapy, patients with acromegaly may continue to suffer from long-term negative self-image and illness perceptions, musculoskeletal pain, and the medical sequelae of the disease (e.g., hypertension) [51–56]. Female sex is widely reported to be associated with worse QOL in patients with acromegaly [57]. Yoshida et al. [58] reported improved QOL in patients who had successful surgical

treatment of acromegaly, compared to that in a control group of patients treated with successful medical therapy without radiotherapy. However, these results have not been widely replicated or reproduced in a randomized, controlled trial.

Summary and Future Directions

QOL in patients with pituitary adenoma is an important consideration despite the "benign" pathology of these tumors. HRQoL is affected by an interplay of surgical factors, disease status, pituitary function, and adverse reactions of treatment. The advent of site- and pathology-specific QOL metrics has allowed surgeons and endocrinologists to better understand specific interventions that may impact QOL. Pituitary surgeons should familiarize themselves with the available QOL instruments and their respective strengths and limitations in order to choose the right scales for their research and patient care. Recent work has demonstrated that patients experience a temporary decrease in QOL associated with surgical intervention that improves to baseline or better levels within 3–6 months after surgery. Future research on modifications of surgical techniques and new surgical instrumentation should focus on further reducing this temporary morbidity. Minimization of sinonasal trauma and avoidance of surgical site complications remain paramount to maximizing patient QOL in the perioperative period.

Acknowledgments The authors thank Dr. Ryan Rehl for providing intraoperative photographs.

Disclosures Andrew S. Little, MD, is an investor in Kogent.

Financial Support None.

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Index

A
Acidophilic stem cell adenomas, 118
Acromegaly
  cabergoline, 374
  combination therapy, 376
  comorbidities, 441
  complications in patients undergoing endoscopic transsphenoidal surgery, 448, 449
  craniotomy, 446
  diagnosis
    advantage of surgical removal, 442
    anatomic diagnosis and staging, 442
    anesthesia pause, 444
    anesthetic issues, 443
    anesthetic precautions, 443
    closure pause, 444, 445
    cortisol levels, 443
    endocrine diagnosis, 442
    growth hormone and prolactin, 442
    hypertension, 443
    IGF1, 442
    laboratory tests, 442
    medical therapy, 442
    pituitary hormones, 442
    preoperative and postoperative coronal MRI scans, 442, 443
    preoperative concerns, 443
    surgical and equipment pauses, 444, 445
    visual symptoms, 442
  endoscopic pituitary surgery, 451–454
  endoscopic transsphenoidal surgery, 447, 448
  GH hypersecretion, 374
  growth hormone, 446
  lanreotide ATG, 374
  macroadenomas, 441
  medical management, 441
  microscopic and endoscopic transsphenoidal surgery, 447, 448
  nasal mucous membranes, 446
  operating microscope/endoscope, 446
  outcomes, 448–450
  pasireotide LAR, 374
  pathologic analysis, patients undergoing endoscopic transsphenoidal surgery, 447, 449
  patient positioning, endoscopic transsphenoidal surgery, 446
  patients referred for postoperative radiation after endoscopic transsphenoidal surgery, 448, 451
  patients undergoing repeat endoscopic transsphenoidal surgery, 447, 450
  pegvisomant, 374, 375
  pituitary adenomas, 441
  pituitary tumors, 447
  postoperative management, 448–450
  principles of skull base surgery, 454, 455
  pseudoencapsulated tumors, 447
  radiation therapy, 441
  SRLs, 375, 376
  SRS, 540, 541, 546, 547, 549, 553
  TSS, 400
  ultrasonic Doppler probe, 447
  vomer, 447
Acromegaly Quality of Life Questionnaire (AcroQoL), 599
ACTH-producing pituitary tumors, 587
ACTH-secreting adenomas, 250, 251, 427, 490
ACTH-secreting microadenomas, 428
ACTH-secreting pituitary adenomas, 566, 567
ACTH-secreting pituitary carcinoma, 589
Adamantinomatous, 404, 405
Adamantinomatous Craniopharyngioma, 134

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7

Adenomas
functioning, 565–572
nonfunctioning, 563, 564
Adjuvant radiation therapy, 406
Adjuvant therapies, 406
Adrenal insufficiency
cortisol level, 66
glucocorticoid replacement, 65, 66
preoperative, 65
steroids, 65
steroid-sparing approaches, 66
Adrenocorticotrophin (ACTH), 582
Airway Issues, 333
Airway management, pituitary tumors surgery, 32, 33
Anesthesia, transsphenoidal surgery
acromegaly, 29, 30
airway management, 32, 33
challenge, anesthesiologist, 38
classification, hormone secretion, 27
cranial nerve palsy, 36
CSF leaks, 36
Cushing's disease, 30
dexmedetomidine, 34
diabetes insipidus (DI), 37
endonasal, sublabial, and endoscopic endonasal, 31
hormones, anterior pituitary, 29
hypopituitarism and postoperative hormone screening, 36
hypoventilation, 31, 32
intracranial neoplasms, 27
lumbar drain, 31
macroadenomas, 27
medical therapy, 28
monitoring, 33
monoclonal adenoma, 27
muscle relaxation, 34
nausea and vomiting, 35, 36
nonfunctioning adenomas, 31
oral airway, 35
pain, 35
positioning and preparation, 33
preoperative assessment, 28
prolactinomas, 28
propofol and sevoflurane, 34
Remifentanil, 34
SIADH, 37
TSH-secreting adenomas, 31
vascular injury, 34
visual field deficits, 36
volatile anesthetics, 34
Anesthesia-related complications
airway issues, 333
cardiac history, 334
intraoperative medication reactions, 334
Invasive Catheters, 331–333
ophthalmic lubricant, 334
Urinary Catheters, 333, 334
Angiographic studies, 518
Angled endoscopes, 420
Anterior cerebral artery (ACA), 206
Anterior communicating artery (ACoA) complex, 411
Anterior cranial fossa (ACF), 208
Anterior gland dysfunction, 329–330
Anterior Skull Base Nasal Inventory (ASK Nasal), 598, 599
Anterior skull base questionnaire (ASBQ), 598
Anti-angiogenic therapy, 589
Anticoagulant and antithrombotic therapy, 502
Antidiuretic hormone (ADH), 360
Apoplexy. *See* Pituitary apoplexy
Arterial epistaxis, 323
ASK nasal inventory, 603

B

Balloon test occlusion (BTO), 421
Basal growth hormone, 450
Beach-chair position, 335
Bicoronal approach, 206
Bifrontal approach
bicoronal approach, 206
burr hole, 205
craniotome, 206
dura, 205
Greenberg retractor, 206
potential advantage, 204
scalp incision, 205
Binostral technique, 432
Biochemical follow-up, 536
Biomarkers
predictive of response, 588–589
Bipolar forceps, 416
Bitemporal hemianopsia, 48, 405

C

Cabergoline, 371, 372, 457, 458
Cabergoline therapy, 374, 375, 459
CAPTEM, 587, 588
Carney complex, 492
Carotid artery, 325
Carotid artery injury, 324, 325
Catastrophes, 317
Catastrophic event, 325

Cavernous sinus, 224, 225, 384, 389, 392, 393, 398, 400, 428, 521
carotid arteries, 152
cranial nerve, 152
ICA, 154
inferior compartment, 158
lateral compartment, 158, 159
medial wall, 156
posterior compartment, 157, 158
roof, 156
superior compartment, 156, 157
Cavernous sinus invasion, 322, 463, 502, 525
Cell-signaling mechanisms, 581
Cerebral ischemia, 505
Cerebrospinal fluid (CSF) leak, 303, 304, 317, 319, 322, 327, 328, 332, 336, 407, 413, 420–423
intraoperative, 348
postoperative, 311, 349
meningitis, 328
repair, 327–328
root causes analysis, 313
transsphenoidal surgery
body mass index (BMI), 303
healing and reconstruction, 304
intraoperative, 303
obesity, 303, 304
postoperative complications, 303
rate, 303
risk, 304
TSS, 396
Chemotherapy
cytotoxic, 583–588
indications, 590
Pituitary Tumors, 591
Chondrosarcoma, 105, 106
Chordoma
Sella turcica and parasellar region tumors, 105
Circle of Willis blood supply, 325
Cisternography, 316
Clivus, 225, 226
Closure methods, transsphenoidal surgery, 303–305
complications, 311–312
CSF leak (*see* Cerebrospinal fluid (CSF) leak)
design, nasal septal flap, 305
lumbar drainage, 311
nasal packing, 311
postoperative imaging, 311
reconstruction, 305
multilayer, 304, 305
vascularized (*see* Vascularized reconstruction)
skull base surgery, 312
vascularized flaps, 309–311
Common nasal endoscopy, 601
Comorbidities, 441
Complex lesions, 278
Complications, transsphenoidal surgery, 316–320, 322, 323
academic or private, 315
anesthesia-related complications, 331–334
cerebrospinal fluid leakage, 327–328
clinic
cisternography, 316
craniopharyngioma, 317, 320
EEA, 317
empty sella, 316, 319
headaches and homogenously enhancing, symmetric pituitary gland, 316–318
hydrocephalus, 316, 318
hyperprolactinemia, 316
macroprolactinemia, 316
MRI, 317, 319
pituitary adenomas, 316
postoperative care, 317
preoperative imaging, 316
prolactin-secreting adenomas, 316
RCCs, 316
sellar arachnoid cyst, 316, 319
closure, 322
cranial nerve injury, 326–327
fat graft harvest site complications, 337
fly-by approach, 321
hypopituitarism, 328–331
minor complications, 331, 332
nasal cavity, 321
operating suite–preincision, 321
oral complications, 336, 337
phases of patient care, 316
pituitary tumor patients, 316
positioning-related issues, 335
postoperative management
inpatient, 322, 323
outpatient, 323
prevention, 315
sinonasal complications, 335–336
sphenoid, 321
surgical microscope, 315
tumor resection, 322
vascular injury, 323–326
video fluoroscopy, 315
Conchal type sinus, 411
Conservative nonsurgical management, pituitary apoplexy, 509
Conventional fractionated radiation, 560

Coronal plane approaches
petrous apex, 286, 287
transcavernous, 286–289
transpterygoid, 285, 286
Corticotroph adenomas, 566, 567
ACTH-secreting adenomas, 122
Crooke's cells, 122
Cushing's disease, 121
histopathology, 122
silent, 123
sporadic, 122
Corticotropic deficiency, 504
Corticotropin-releasing hormone (CRH), 384
Cranial nerve deficits, 574
Cranial nerve injury, 326–327
Cranial nerve palsy, 505
Cranial Neuropathy, SRS, 550–551
Craniopharyngeal duct, 404
Craniopharyngiomas, 53, 101, 317, 320, 412–422, 487
adamantinomatous, 133, 134, 404, 405
bitemporal hemianopsia, 405
calcification, 407
children and adolescents, 133
classification, 409–412
craniopharyngeal duct, 404
CT imaging, 408
cystic and solid components, 404
DI, 405
endocrinologic assessment, 407
endoscopic endonasal transsphenoidal approach, 405–407
endoscopic endonasal transsphenoidal surgical technique (*see* Endoscopic endonasal transsphenoidal surgical technique)
epithelial tumors, 403
GC treatment, 407
genetic mutation, 134
hydrocephalus, 405
intracranial neoplasms, 133
MRI, 407
multiple hypothalamic-pituitary axis deficiency, 405
neural tube process, 404
papillary, 134, 135, 404, 405
pathological classification, 116
pediatric disease, 404
pituitary and sellar region, 114
postoperative care, 422–423
preoperative evaluation, 407–408
preoperative planning, 409–412
suprasellar and intrasellar components, 404
suprasellar location, 404
suprasellar, 133
symptoms, 405
T1 weighted imaging (WI), 407
T2WI, 408
thyroid hormone, 407
treatment strategy, 405–407
types, 404
variants, 133
wet keratin, 404
WHO grade I tumors, 404
Craniopharyngiomas (CP), 492, 494
Craniotomy, 446
Cranio-vertebral junction (CVJ), 225, 226
CRH-stimulation test, 532
Crooke cell tumor, 582
Crooke's cell adenomas, 122
CSF rhinorrhea, 495, 497
Cushing's disease, 50, 427–430, 432–435, 490, 491, 532, 599–601, 605
ACTH-secreting adenoma, 67
anesthesia, 30
cabergoline, 369, 371, 372
cabergoline and pasireotide, 368
combination therapy, 373
decision for surgery, 431
definition of remission, 67
endoscope *vs.* microscope techniques, 435, 436
etomidate, 369, 371
ketoconazole, 370
medical therapy, 369
metyrapone, 369, 370
mifepristone, 369, 373
mitotane, 369, 371
pasireotide, 369, 372
post-op, 436
postoperative steroids, 67
preoperative difficulties, 431–432
preoperative evaluation
ACTH-secreting adenomas, 427
ACTH-secreting microadenomas, 428
cavernous sinus, 428
CT, 428
diagnosis, 427, 429
endocrine testing, 427
endocrinological studies, 429
hypercortisolemia, 427
inferior petrosal sinus, 429, 430
IPSS, 428–430
MRI, 427, 429
petrosal sinus sampling, 429
post-IPSS brainstem stroke, 430
tumor detection, 428

SRS, 540, 541, 547, 553, 554
steroidogenesis inhibitors, 368, 369
surgical indications, 431
surgical techniques (*see* Surgical resection, Cushing's disease)
TSR, 368
TSS, 399
CushingQoL, 599, 600
CyberKnife, 559, 562
Cysts, 54
Cytotoxic chemotherapy, 581
5-FU/CCNU, 584
aggressive/malignant pituitary tumors, 583
clinical and radiographic responses, 584, 586
clinical utility, 583
glioblastoma, 588
interferon, 584
luteinizing hormone (LH), 586
luteinizing-hormone-secreting pituitary adenoma, 584
mechanisms, 586
meta-analysis, 586, 587
MGMT, 585
outcomes, 583
prolactin-secreting pituitary adenoma, 584
radiographic response rate, 587
temozolomide, 584, 586–588
temozolomide mechanism of action, 584, 586
treatment of invasive pituitary tumors, 583

D
DDAVP, 329, 330, 332
Delayed symptomatic hyponatremia, 533, 534
Dermoid and epidermoid cysts, 109
Dermoid cysts, 109
Diabetes insipidus, 422
Diabetes insipidus (DI), 37, 317, 329, 405, 533, 536
postoperative clinical course
ADH, 64
hyponatremia, 64
pharmacological treatment, 64
recovery, 65
triphasic response, 63
preoperative care
adaptation of neurohypophyseal function, 61
ADH release, 61
ADH secretion, 61
deficit of ADH action, 62
diagnosis, 62, 63
outcomes, 61
plasma osmolality, 61
surgical, 62
symptom, 61
Diaphragma sellae, 409
DNA mismatch repair protein, 589
DNA-repair enzyme MGMT, 588
Dopamine agonist therapy, 458, 459, 465
Dopamine agonists, 581
Dual antiplatelet therapy, 422
Dumbbell-shaped tumors, 525

E
Empty sella, 316, 319
Endocrine diagnosis, 442
Endocrine dysfunction, 504
Endocrine testing, 427
Endocrinologic assessment, 407
Endocrinology evaluation, 46–47
Endonasal approach
sublabial, 387
transsphenoidal approach, 398
Endonasal skull base surgery, 345
Endonasal transsphenoidal surgery, 531
Endoscope *vs.* microscope techniques
Cushing's disease, 435
Endoscopic approach
bimanual-binarial dissection, 390
complications, 396–398
CSF leaks, 394, 395
image guidance, 393, 394
ostium, 390
postoperative care, 389, 395
sellar phase, 392
sphenoid sinus exploration, 391
sphenoidotomy, 391
tumor removal, 392, 393
Endoscopic endonasal approach (EEA), 517, 519, 521, 525
extensive lesions, 296
infradiaphragmatic craniopharyngioma, 221
intrasellar pituitary macroadenoma, 220
nasal septal flap, 220
neuronavigation system, 219
patient positioning, 222
sagittal plane approaches, 279, 280, 282–284
sagittal plane, 278–285
surgical instrumentation, 220–222
Endoscopic endonasal transsellar approach, 525

Endoscopic endonasal transsphenoidal (EET) approach
giant pituitary adenomas, 525–527
and treatment strategy
adjuvant radiation therapy, 406
EET approach, 406, 407
fluoroscopic image guidance, 406
hypothalamic or pituitary injury, 406
intracystic infusion, 406
operating microscope, 406
retraction, 406
surgical intervention, 405
Endoscopic endonasal transsphenoidal surgical technique, 412–422
craniopharyngiomas
intraoperative complication, 421–422
nasal exposure, 413–414
one-handed technique, 412
otolaryngologist, 412
positioning, 413
preinfundibular, 417–418
preparation, 413
reconstruction, 420–421
retroinfundibular, 419–420
sinus exposure, 413–414
skull base exposure, 415
transinfundibular, 418–419
tumor resection, 415–417
Endoscopic pituitary surgery, 451–454
acromegaly
anesthesia consult prior to surgery, 452
assess for and address comorbidities, 451
diagnosis, 451
mucous membranes, 453
postoperative management, 454
pretreatment with somatostatin analogs to alleviate comorbidities, 451, 452
reduce size of tumors, 451, 452
sellar phase, 453
surgical anatomy, 453
surgical aspects, 453
Endoscopic transsphenoidal approach, 525
rhinological complications, 345
sphenoid sinus, 354
Endoscopic transsphenoidal pituitary surgery (ETPS), 248–251
complication rate, 246–248
CSF leaks, 252
diabetes insipidus (DI), 254
endocrinopathies, 253, 254
endonasal skull-base surgery, 252
functional adenoma (*see* Functional adenomas)
internal carotid artery, 253
neurologic complications, 253
nonfunctional adenomas, 246–248
optic nerves and chiasm, 253
orbital/retro-orbital hematomas, 253
suprasellar extension, 253
vascular injury, 252
visual symptoms, 246
Endoscopic transsphenoidal surgery, 213
reconstruction techniques, 226
skull base (*see* Skull base)
Endoscopic *vs.* microscopic transsphenoidal surgical approach, 602, 603
Endovascular sacrifice, ICA, 421
Epidermoid, 108
Epistaxis, 535
Epithelial tumors, 403
Ethmoidal planum, 223, 224
Etomidate, 371
Extended endonasal approaches, 317
Extended endoscopic endonasal transsphenoidal (EEET) approach, 413, 415
External Beam Radiation Therapy (EBRT) *vs.* Radiosurgery for Management of Pituitary Adenomas, 551, 552

F

Familial isolated pituitary adenoma (FIPA) syndrome, 114
Fat graft harvest site complications, 337
Flap necrosis, 312
Fluid and sodium issues, 330, 331
Fluid attenuated inversion recovery (FLAIR) sequences, 408
Fluoroscopy/intraoperative navigation tools, 432, 433
Fly-by approach, 321
Fractionated (conventional) radiation, 559
Fractionated radiation therapy, 561, 562, 565
Fractionation, radiation therapy, 559–560
Frontotemporal transcranial routes, 517
Functional adenomas
acromegaly, 249, 250
Cushing's disease, 250, 251
endocrinologic cure (EC), 248
prolactinomas, 248, 249
Functional pituitary adenomas, 605, 606
Functioning adenomas
categorization, 565
corticotroph adenomas, 566, 567
fractionated radiation therapy, 565
lactotroph adenomas, 568–572

radiotherapy, 565
somatotroph adenomas, 566–570
SRS, 565
symptoms, 565

G
Gamma Knife radiosurgery (GKRS), 540, 559, 560
Gasket seal, 421
Gasket seal component, 421
Germ Cell Tumors
Sella turcica and parasellar region, 104–105
Germinoma, 105
GH deficiency, 504
GH secreting adenomas, 249, 250
Giant adenomas, 517, 519, 525
Giant pituitary adenomas
acute hydrocephalus/optic nerve compression, 519
bilateral visual loss, 519, 520, 522
definitions, 517
endoscopic endonasal approaches, 517, 519
endoscopic endonasal transsphenoidal surgery, 525–527
incomplete removal, 519
management, 517
management strategy, 521–525
medical therapy, 517
microscopic transsphenoidal surgery, 525–527
open transcranial approaches, 527
open transcranial routes, 521
preoperative planning, 518–519
preoperative radiological assessment and planning, 519
radiation therapy, 517
radical resection, 517
surgical goals, 518–519
surgical management, 517
surgical risks, 519
transsphenoidal approach, 521
vascular complications risk factors, 519
Gliadel wafers, 584
Glioblastoma, 588
Glucocorticoid receptor antagonists. *See* Mifepristone
Glucocorticoids (GC) treatment, 407
Gonadal and growth hormone, 423
Gonadotroph adenomas, 572
chromophobic cells, 124
diagnosis, 124
gonadotropins, 123
Luteinizing Hormone (LH), 123
nonfunctioning tumors, 123
steroidogenic factor 1 (SF-1), 124
Gonadotropin-producing pituitary adenomas, 583
Granular cell tumors (GCTs), 131, 132
Growth hormone secreting tumors, 491–493, 500
Growth hormone–secreting lesions, 441
Growth hormone–secreting microadenomas approach, 450
Growth hormone–secreting pituitary adenomas, 441, 566–570

H
Headache, 503, 504
Health-related QOL (HRQoL) scales
KPS, 597
SF-12, 598
SF-36, 598
High-dose glucocorticoids, 508
Hormonal imbalance, 46, 47
Hormonal therapy, 581
Hormone-active pituitary tumors, 487, 496
Hybrid approach, 168, 169
Hydrocephalus, 316, 318, 405
Hypercortisolemia, 427, 432, 435, 605
Hyperlipidemia, 443
Hyperphagia, 422
Hyperprolactinemia, 316, 459
Hypertension, 443
Hypofractionation, 562
Hypointense mass, 51
Hypophysectomy, 434
Hypopituitarism, 360, 503, 563, 573, 600
ACTH, 361
ADH, 362
anterior gland dysfunction, 329–330
DI, 329
diabetes insipidus, 365
diagnosis, 361
estrogen replacement, 365
fluid and sodium issues, 330, 331
GH deficiency, 365
glucocorticoid, 362, 363
hypersecretion syndromes (*see* Hypopituitarism)
management, 363
sex steroid production, 364, 365
sex steroid replacement, 365
SIADH, 329
thyroid hormone, 364
transsphenoidal resection, 366

Hypopituitarism and hypothalamic dysfunction, 550
Hypothalamic injury, 396
Hypothalamic Pilocytic Astrocytoma, 104
Hypothalamic/pituitary injury, 406
Hypothalamic-pituitary-adrenal (HPA) axis deficiency, 407

I
IGF1, 442
IGF-I falls, 449
Inexperienced practitioners, 459
Inferior petrosal sinus, 430
Inferior petrosal sinus sampling (IPSS), 428–430
Infundibular/Hypothalamic Tumors, 53
Infundibulum, 329, 409
Intensity-modulated radiation therapy, 561
Intercavernous sinus bleeding, 416
Interferon, 584
Internal carotid arteries (ICAs), 411, 412
  cavernous sinus, 154, 155
  injuries, 421
  parasellar, 154
Interpeduncular cistern. *See* Retrosellar region
Intraoperative complication
  craniopharyngiomas, 421–422
Intraoperative imaging, pituitary surgery, 260–269
  craniotomy approaches, 259
  CT, 269, 270
  fluorescence imaging technique, 270
  implementation, 271
  incomplete tumor resection, 259
  intracranial neoplasms, 259
  iUS, 270
  MRI (*see* Intraoperative MRI, pituitary surgery)
  neurosurgery, 259
  nonradiographic, 270
  quality assurance, 260
Intraoperative MRI (iMRI), 263–265, 393, 394
  adenoma resection, 260
  and endoscopy, 266–268
  cost-effectiveness, 268
  EOR, 260
  high-field iMRI, 260
    advantages, 265
    Brainlab^{tm}, 263
    movable magnet, 264
    performence, 265
  limitations, 268
  low-field iMRI, 260–263
  magnet, 260
  management, 260
  multimodality image integration, 265, 266
  nonfunctioning pituitary macroadenoma, 267
  operating room equipment, 261
  process, 266
  risk, 260
Intraoperative ultrasound (iUS), 270
Intrasellar pressure, 499
Invasive catheters, 331–333

J
Jules Hardy endocrine-active microadenomas, 21

K
Karnofsky Performance Scale (KPS), 597
Kerrison rongeur, 416
Ketoconazole, 370

L
Lactotroph adenomas, 568–572
  acidophilic stem cell, 118
  densely and sparsely granulated variants, 117
  dopamine agonists, 118
  medium-sized cells, 117
  men and elderly women, 117
  microadenoma, 116
  perivascular and interstitial tumoral fibrosis, 118
  prolactinomas, 116
  sporadic tumors, 117
Lactotroph hyperplasia, 502
Late Adverse Radiation Effects, 551
Lateral opticocarotid recess (lOCR), 415
Lateral recess of the sphenoid sinus (LRSS), 225
LINAC-based stereotactic treatment, 562
Linear accelerator (LINAC)
  SRS, 561
Linear accelerator-based stereotactic radiosurgery, 559
Linear accelerator-based stereotactic radiosurgery (LINAC-based SRS), 561
Luteinizing hormone (LH), 586
Luteinizing-hormone-secreting pituitary adenoma, 584

M
Macroadenomas, 100, 441, 459, 460, 462, 504
Macroprolactinemia, 316
McCune–Albright Syndrome, 492
Medial opticocarotid recess (mOCR), 415, 416
MEDPOR, 421
Meningiomas, 53, 102, 103
Metastatic disease, 54
Metyrapone, 370
MGMT, 585–590
Microadenomas, 99, 459, 533
micro-Doppler, 325
Microprolactinomas, 460, 462
Microscopic transsphenoidal approaches, 525
Microscopic transsphenoidal surgery, 525
  giant pituitary adenomas, 525–527
Microsurgical approach, 168
Middle turbinate resection, 604
Mifepristone, 373
Minor Endocrine Issues, 330
Mitotane, 371
Morbidity and efficacy of medical therapy, 600, 601
mTOR, 590, 591
mTOR inhibitor, 590
Multiple endocrine neoplasia (MEN), 588
Multiple hypothalamic-pituitary axis deficiency, 405

N
Nasal crusting, 93
Nasal exposure, 413–414
Nasal functions and physiology, 88
Nasal morbidity, 464
Nasal mucous membranes, 446
Nasal packing, 535
Nasoseptal flaps, 414, 421, 603, 604
Neural tube process, 404
Neuro-anatomy, 72–74
Neuro-ophthalmic evaluation, 71, 80–82
  acute vision loss, 71
  cavernous sinus, 83
  cavernous sinus lesions, 84
  complications of Sellar Tumors, 83–84
  compression, optic nerves, chiasm, or tracts, 85
  color vision, 74
  endocrinopathy, 71
  fundus examination, 79–80
  Goldmann kinetic perimetry, 79
  hemifield slide phenomena, 76
  Humphrey visual field report, 78
  large macroadenoma, 82
  OCT, 80, 81
  ophthalmoplegia, 85
  optic chiasm, 72
  optic chiasm and visual symptoms, 72–74
  pattern of visual field loss, 79
  perimetric assessment, visual fields, 71, 77–79
  postfixation blindness, 75
  RAPD signifies asymmetric impairment, 74
  reduction in visual acuity, 74
  severe visual loss, 84
  Snellen visual acuities, 74
  vertical displacement, optic chiasm, 73
  visual acuities, 75
  visual loss
    management, 80–82
    postoperative, 82
Neuro-ophthalmic evaluation, postfixation blindness, 75
Neuro-ophthalmology, 47, 48
Non-ACTH-secreting pituitary adenomas, 490
Non-cell-cycle-specific apoptosis, 584
Nonfunctional adenomas, 246, 248
Nonfunctional pituitary adenomas (NFPAs), 500
Nonfunctioning adenomas
  anesthesia, 31
Nonfunctioning pituitary adenomas, 472–474, 476–480, 489, 526, 527, 563, 564
  annual MRI or CT scans, 481
  anterior hypopituitarism, 471
  Coronal T1-weighted postcontrast MRI, 482
  cystic, 481
  DI, 471
  gonadotropins, 471
  neurologic symptoms, 471
  nonsurgical options
    apoplexy, 474
    bromocriptine, 473
    macroadenomas, 474
    metastases, 474
    microadenomas, 474
    optic chiasm, 474
    size or hormonal function, 474
    treatment strategy, 474
  pituitary apoplexy, 471
  postoperative complications, 478
  postoperative DI, 482
  postoperative evaluation, 481
  postoperative radiotherapy, 481
  preoperative evaluation
    hormone deficit, 473
    microadenomas and low testosterone, 473
    MRI and CT scans, 472
    pituitary-gonadal axis, 473

Nonfunctioning pituitary adenomas (*cont.*)
prolactin level, 473
prolactinoma, 473
radiotherapy, 480, 481
recurrence
ACTH, 479
Cushing's disease, 479
cystic or posthemorrhagic changes, 479
intraoperative MRI, 479
null cell or gonadotropin-producing, 479
risk, 479
silent adenomas, 480
"silent" corticotroph, 479
somatotroph, 479
survival rate, 478
recurrence rate, 481
Sagittal postcontrast CT, 472
Sagittal T1-weighted postcontrast MRI, 472
surgery
apoplexy, 477
complications, 477
CSF leak, 477
growth of, 476
invasion, cavernous sinus, 476
mortality, 477
radiotherapy, 476
size "limit", 477
sublabial or endonasal approach, 477
symptomatic, 476
transcranial approach, 476
transsphenoidal or transcranial removal, 477
visual function, 477
treatment, 481
treatment algorithm, 475
Nonfunctioning pituitary adenomas (NFPAs), 384
Nonfunctioning tumors, 52
Nonpituitary suprasellar pathology, 536
Nonradiographic intraoperative imaging modalities, 270
Nonsurgical factors, QOL, 600, 601
pituitary adenomas
hypopituitarism, 600
morbidity and efficacy of medical therapy, 600, 601
Normoprolactinemia, 459
Null cell adenomas
chromophobic, 125
immunohistochemical assays, 125
immunoreactive, 125
mass lesion, 125
pituitary hormones, 125
transcription factors, 125
ultrastructural analysis, 125

O

Olfaction, 604, 605
Ondi cells, 412
Oophorohysterectomy, 460
Open transcranial approaches
giant pituitary adenomas, 527
Ophthalmic lubricant, 334
Optic chiasm, 409, 560
Optic chiasm and pituitary infundibulum, 326
Optic nerves (ONs), 409
Optical coherence tomography (OCT), 80, 81, 442
Oral Complications, 336, 337
Orbitozygomatic (OZ) approach, 201, 202
Otolaryngologist, 412

P

Panhypopituitarism, 328, 434
Papillary craniopharyngiomas, 135, 404, 405
Paranasal sinus function and physiology, 88
Parasellar tumors, 317, 487, 492, 497
Pasireotide, 372, 590
Patient-reported sinonasal quality of life (QOL), 602
Pediatric Cushing's disease, 490, 491
Pediatric endonasal surgery, 488
Pediatric patients
complications of transsphenoidal surgery, 495
CP, 492–495
craniopharyngioma, 487
hormone-active pituitary tumors, 487, 496
parasellar tumors, 487
pituitary adenomas, 489–492
surgical interventions, 487
surgical outcomes, 487, 490, 492
in transsphenoidal surgery, 487, 488
Pediatric" disease, 404
Pegvisomant, 375
Perioperative care, pituitary patients, 65–67
adrenal insufficiency (*see* Adrenal insufficiency)
Cushing's disease (*see* Cushing's disease)
Permanent diabetes insipidus, 328
Petrous apex, 286, 287, 293
PIK3/mTOR inhibitors, 590
Pilocytic astrocytoma, 104
Pituicytoma
adults, 130
grossly soft, 131
immunohistochemistry, 131
mitotic activity, 131
neuroimaging, 130

Rosenthal fibers and eosinophilic granular bodies, 131
tan lesions, 131
Ultrastructural features, 131
Pituitary adenoma
acromegaly therapy (*see* Acromegaly)
ADH, 360
Cushing's diseases (*see* Cushing's disease)
diagnosis, 366, 367
high prevalence, 531
hormone secretion, 359–361
hypersecretion syndromes, 359
prolactinoma, 367, 368
sella turcica and parasellar region
adrenocorticotropic-secreting, 98
cavernous sinus invasion, 100
ectopic adenomas, 98
intrasellar mass, 98
macroadenomas, 99
microadenomas, 98, 99
prolactinomas, 98
prolactin-secreting adenomas, 98
stalk, suprasellar cistern, 98
TSH, 377
Pituitary adenomas, 116–118, 121, 123, 125, 316, 595
corticotroph (*see* Corticotroph adenoma)
cytodifferentiation, 115
development, 113
functioning, 115, 565
gonadotroph, 123, 124
gonadotroph and null cell adenomas, 116
gonadotropic adenomas, 572
growth hormone–secreting, 441
growth hormone–secreting lesions, 441
growth hormone–secreting pituitary adenomas, 441
growth hormone–secreting tumors, 491–493
hereditary conditions, 114
hyperfunctioning, 441
Lactotroph (*see* Lactotroph adenomas)
nonfunctioning, 115, 489, 563, 564
nonsyndromic gigantism, 114
oncogene *PTTG*, 114
pediatric Cushing's disease, 490, 491
plurihormonal (*see* Plurihormonal adenomas)
prolactinomas, 489–490
QOL (*see* QOL in pituitary adenomas)
somatotroph, 118–120
sporadic, 114
thyrotroph (*see* Thyrotroph adenomas)
thyrotropic adenomas, 572
transcription factors, 115
treatment, 446
USP8 gene, 114
WHO classification, 115
Pituitary apoplexy
acute neurosurgical evaluation, 500
cardiac surgery, 502
characterization, 499
clinical features, 505
clinical presentation, 503
altered consciousness, 505
endocrine dysfunction, 504
headache, 503, 504
visual symptoms, 505
clinical syndrome, 499
CT, 506
description, 499
development, 501
diagnostic evaluation, 502
differential diagnosis, 505, 506
dynamic hormone testing, 502
epidemiology, 500
etiology, 500–501
GnRH, 502
intrasellar pressure, 499
magnetic resonance angiography, 506
management
conservative nonsurgical management, 509
high-dose glucocorticoids, 508
operative management, 508, 509
surgical *vs.* conservative, 508
medical factors, 503
MRI, 506–508
neurosurgical and endocrine services, 500
nonspecific symptoms, 505
optimal management, 500
outcome, 500
pathology, 509–511
pathophysiology, 500–501
pituitary adenoma, 499
postoperative care, 510, 511
precipitating factors, 501–503
radiotherapy, 502
sella turcica and parasellar region tumors, 100
sellar tissue volume, 499
therapeutic management, 502
TRH, 502
Pituitary Apoplexy, 52
Pituitary blastoma
DICER1 syndrome, 128
histopathology, 128
primitive malignant neoplasm, 128

Pituitary carcinomas
characteristics, 127
histopathology, 127, 128
mechanisms of progression, 127
metastases, 127
sellar tumor, 127
Pituitary dysfunction, 322
Pituitary gigantism, 492
Pituitary macroadenomas, 518
Pituitary mass, 49
Pituitary neuroendocrine tumors, 128
pituitary blastoma (*see* Pituitary blastoma)
pituitary carcinoma, 127, 128
tumor grading, 126
Pituitary non-neuroendocrine tumors, 130, 131, 133–135
craniopharyngioma (*see* Craniopharyngioma)
diabetes insipidus, 129
differential diagnosis, sellar masses, 129
GCTs, 131, 132
low-grade, 129
pituicytoma (*see* Pituicytoma)
SCOs, 132
Pituitary surgery, 5, 6, 12–14, 433, 509
developments, surgery, 11
endoscopy, 6
endoscopy, transsphenoidal surgery, 5–6
frontotemporal craniotomy, 3
high risk of mortality, 1
hypophysectomy, 3
microneurosurgery, 3
microscopic and endoscopic approaches, 1
sella turcica, 2
subtemporal approach, 2
surgical approach, 1
transcranial surgery
cranial approach, 12
decompressive procedures, 12
German surgeon-anatomist, 12
Krause's approach, 12
mid-twentieth century, 14
nineteenth century operations, 13
pituitary gland, 14
pituitary pathology, 12
resection, 1889, 12
transsphenoidal approach, 1, 2
Pituitary tumors, 27, 487, 559
adrenocorticotrophin (ACTH), 582
anesthesia (*see* Anesthesia, transsphenoidal surgery)
anti-angiogenic therapy, 589
biomarkers, 588–589
cell-signaling mechanisms, 581
chemotherapy, 590
cytotoxic chemotherapy, 581, 583
dopamine agonists, 581
Endoscopic Pituitary Surgery, 22
Extended Trans-sphenoidal Surgery, 22–23
hormonal therapy, 581
hormone-active, 487, 496
Image Guidance and Intraoperative MRI, 21–22
malignant behavior, 582
molecular mechanisms, 582
in pediatric patients (*see* Pediatric patients)
pituitary carcinomas, 582
radiation therapy (*see* Radiation therapy)
subtypes and biologic characteristics, 582
targeted therapy, 589–590
trans-sphenoidal surgery, 14–15
Pituitary/parasellar surgery
inferior turbinate/lateral nasal wall flap, 309–311
middle turbinate flap, 309
Planum sphenoidale, 406
Plurihormonal adenomas
combinations, 126
plurihormonal Pit-1-positive adenomas, 126
symptoms, 125
Pneumatization, 412, 415, 488, 489
Polestar™, 262
Positioning-related issues, 335
Posterior cerebral arteries (PCAs), 411
Posterior ethmoidectomy, 412
Postfixation blindness, 75
Post-IPSS brainstem stroke, 430
Postoperative care
craniopharyngiomas, 422–423
DDAVP formulations, 65
DI and SIADH (*see* Diabetes insipidus (DI))
hormonal analysis
ACTH-producing pituitary adenomas, 60
awareness, 59
deficiencies, 60
hypersecretion, 60
physical examination and history, 59
prolactin measurement, 60
pituitary apoplexy, 510, 511
transsphenoidal pituitary surgery, 67
Postoperative endocrinological complications, 496
Postoperative hormone testing
Cushing's disease, 532
growth hormone levels, 532
IGF-1, 532
imaging, 534
sodium and water homeostasis, 533–534

Postoperative management, 532–536
endonasal transsphenoidal surgery, 531
inpatient
postoperative hormone testing, 532–534
postoperative steroids, 532
outpatient
biochemical follow-up, 536
sinonasal corridor, 534–535
visual field testing, 535
patient's pathology, 531
pituitary adenoma, 531
Postoperative steroids, 532
Prechiasmatic tumors, 409
Preinfundibular craniopharyngiomas, 417–418
Preinfundibular tumors, 408, 411
Preoperative assessment, 28
anesthesia (*see* Anesthesia, transsphenoidal surgery)
Preoperative evaluation, 88
compression, 45
craniopharyngiomas, 407–408
hypopituitarism, 45
mass effect, 43
radiological diagnosis, 43–45
rhinologic (*see* Rhinologic evaluation)
Preoperative planning, 408–412
craniopharyngioma classification
ACoA complex, 411
conchal type sinus, 411
diaphragma sellae, 409
EET approach, 411
ICAs, 412
infundibulum, 409
optic chiasm, 409
optic nerves (ONs), 409
pneumatization, sphenoid sinus, 412
posterior ethmoidectomy, 412
prechiasmatic tumors, 409
preinfundibular tumors, 408, 410, 411
preoperative CT imaging, 411
retrochiasmatic tumors, 409
retroinfundibular tumors, 410, 411
sellar type sinus, 411
Sphenoid sinus type, 411
third ventricle, 409
third ventricular tumors, 410
transinfundibular tumors, 409–411
types, 410
volume-acquisition T1WI contrast-enhanced MRI sequences, 411
Prepubescent girls, 489
Primary treatment modality, 464, 465
Prognostic factors, prolactinomas
cavernous sinus invasion, 463
clinical series, 462
demographics and outcomes, 460, 462
evidence of tumor invasion, 460
macroadenomas, 462
microprolactinomas, 460, 462
patient selection, 463
pseudocapsular resection, 462
surgical experience, 460, 462
surgical techniques and technologies, 462
tumor size, 460
Prolactinomas, 28, 48, 249, 458–460, 489, 490, 500, 568–572, 582
assessing postoperative remission, 463
cabergoline, 457
demographics and outcomes, 460–462
medical management
cabergoline, 458
cardiac valvular insufficiency, 460
dopamine agonist therapy, 458
familial syndromes, 460
high response rate, 459
higher doses, 459
hyperprolactinemia, 459
inexperienced practitioners, 459
infertility and pregnancy, 459
lack of tumor reduction, 459
normoprolactinemia, 459
oophorohysterectomy, 460
side effects, 459
stalk effect-related hyperprolactinemia, 459
therapeutic goals, 458
morbidity and mortality, 463, 464
patient selection, 457
primary treatment modality, 464, 465
prognostic factors, 460–463
surgical expertise, 458
surgical treatment, 457
symptoms, 457
Prolactinomas, SRS, 540, 546, 549, 553
Prolactin-secreting adenomas, 316
Prolactin-secreting pituitary adenomas, 489, 568–572, 584
Prophylactic antibiotics, 535
Proton beam therapy, 562, 563
Proton radiation therapy, 559
Pseudocapsular resection, 462
Pseudocapsular resection technique, 462
Pseudocapsule, 433
Pseudoencapsulated tumors, 447

Pterional approach
anterior and middle cranial fossa, 194
bovie electrocautery, 194, 195
carotid artery and optic nerve, 200
craniotomy, 195
disadvantage, 201
dural flap, 196
myocutaneous scalp flap, 196, 197
olfactory tract, 196, 198
STA, 194, 195
sylvian fissure, 198, 199
Pterygopalatine fossa (PPF), 285

Q
Quality of life (QOL) in pituitary adenomas
assessment, 595
concept, 596
definition, 595
functional pituitary adenomas, 605, 606
health-related QOL (HRQoL), 595–598
instruments, 597
metrics, 596
nonsurgical factors, 600–601
outcome, 596
site- and disease-specific QOL scales, 598–600
surgical factors, 601–605

R
Radiation therapy
cranial nerve deficits, 574
CyberKnife, 562
fractionation, 559–562
functioning adenomas, 565
GK, 560
hypopituitarism, 573
LINAC-based SRS, 561
neurologic symptoms, 572
nonfunctioning pituitary adenomas, 563–565
proton beam therapy, 562, 563
secondary tumors, 572, 574, 575
single radiation technique, 559
strokes, 575
treatment modality, pituitary adenomas, 559
visual deficits, 572
visual pathway injury, 574
Radiation-based adjuvant therapies, 534
Radiosurgery, 540
SRS (*see* Stereotactic radiosurgery (SRS))
Rathke's cleft cysts (RCCs), 108, 316
Rathke's pouch, 404
Redundant flap, 414
Rescue flap, 324
Rescue flap approach, 323
Retrochiasmatic tumors, 409
Retroinfundibular craniopharyngiomas, 419–420
Retroinfundibular tumors, 410, 411
Retrosellar region
cranial nerves, 163
vasculature, 163
Rhinologic evaluation
microscopic sublabial approaches, 87
nasal functions and physiology, 88
paranasal sinus function and physiology, 88
postoperative
CSF leaks, 92, 93
endonasal skull base surgery, 92
intraoperative bleeding, 92
nasal crusting, 93
procedure, 92
septal deviation, 89
septal perforations, 93
sinonasal quality of life, 93
twisted nose, 91
preoperative
active bacterial sinusitis, 88
concha bullosa, 89
concomitant septal deviation, 89
CT angiography, 92
CT scan, 91
endoscopic assessment, 88
history of sinonasal conditions, 88
MRI images, 91
nasal anatomy, 89
Saddle nose deformity, 90
septal deviation, 89
sleep apnea, 91
twisted nose deformity, 90
transnasal transsphenoidal approach, 87
Rhinological complications
acute rhinosinusitis, 352, 353
chronic rhinosinusitis, 354, 355
crusting, 350, 351
CSF, 348
endoscopic transsphenoidal surgery, 345
nasal vestibule burns, 349
olfaction loss, 355, 356
perioperative management, 346
postoperative management, 349, 350
sinusitis, 351–353
synechiae, 351, 352
vascular perioperative complications, 346–348
Rhinological evaluation, 46

S
Saddle nose deformity, 90
Sagittal plane approaches
  transclival, 282, 283
  transcribriform corridor, 280
  transodontoid, 283–285
  transplanum transtuberculum, 280–282
  transsellar, 279, 280
Salvage *vs.* adjuvant radiation, 563
Sarcoidosis, 107
Schwannomas, 103
Secondary tumors, 574, 575
Sella turcica, 1, 2, 6, 54, 427, 433
Sella turcica and parasellar region, 95–97, 99–109
  cysts
    Dermoid cysts, 109
    epidermoid cyst, 108
    Rathke's cleft cyst, 108
  diagnoses, 95
  empty sella, 110
  imaging anatomy
    cavernous sinuses, 96
    midline depression, sphenoid bone, 95
    pituitary gland, 95, 96
    sella turcica, 96
  imaging protocol
    coronal and sagittal T1-weighted postcontrast images, 96
    coronal T1-weighted images, 97
    CT, 96
    MRI, 97
  intracranial hypotension, 109, 110
  Langerhans cell histiocytosis, 107
  MRI, 98
  Operative Planning, 110
  pituitary gland, MRI, 97
  postoperative imaging evaluation, 111
  tumors, 98
    chondrosarcoma, 105, 106
    craniopharyngioma, 101
    germinoma, 104, 105
    Hypothalamic Pilocytic Astrocytoma, 104
    LCH, 106
    macroadenoma, 100
    meningiomas, 102, 103
    microadenoma, 99
    neurosarcoid, 107
    pilocytic astrocytoma, 104
    pituitary adenoma (*see* Pituitary adenoma)
    pituitary apoplexy, 100
    sarcoidosis, 107
    Schwannomas, 103
    tuber cinereum hamartoma, 102
Sella, skull base, 390
Sellar and parasellar reconstructions
  autologous fat graft, 304
  flow leaks, 304
  "gasket seal" technique, 304
  mucosal grafts, 304
  nonvascularized reconstruction technique, 305
  sphenoid with adipose tissue, 304
  technique, 304
  vascularized, 305–308
Sellar arachnoid cyst, 316, 319
Sellar masses, 59
Sellar meningioma, 54
Sellar phase, 453
Sellar region, 145–147, 149, 151–163
  cavernous sinuses (*see* Cavernous sinus)
  diaphragma sellae, 151–152
  pituitary gland, 151
  retrosellar lesions (*see* Retrosellar region)
  sphenoid bone
    anatomy, 149, 151
    miscellaneous anatomy, 147, 149
    osseous anatomy, 145–147
  suprasellar lesions (*see* Suprasellar region)
Sellar tissue volume, 499
Sellar tumors, 488, 492, 494
Sellar type sinus, 411
12-Item Short Form Health Survey (SF-12), 598
2006 Pituitary Society guidelines, 458
36-Item Short Form Health Survey (SF-36), 597, 598, 600, 604
Silent corticotroph adenomas, 582
Single radiation technique, 559
Sinonasal complications, 335–336
Sinonasal Corridor, 534–535
Sino-Nasal Outcome Test, 599
Sinus exposure, 413–414
Site- and disease-specific QOL scales
  AcroQoL, 599
  ASBQ, 598
  ASK Nasal, 598, 599
  CushingQoL, 599, 600
  Sino-Nasal Outcome Test, 599
Skull base, 278–289
  anterior, 214, 215
  complications, 296
  coronal plane (*see* Coronal plane approaches)
  cranio-facial approaches, 213
  endoscopic endonasal corridors (*see* Endoscopic endonasal approach (EEA))
  middle, 215–218

Skull base (*cont.*)
patient positioning, 289
posterior, 217–219
reconstruction, 294–296
sagittal and coronal planes, 278
transsphenoidal approach, 277
Skull base exposure
and tumor resection, 415
Skull base neurovascular structures, 525
Skull base surgery
principles, 454, 455
Small sellar subdiaphragmatic tumors, 413
SNOT-22, 597, 599, 602–604
Sodium and water homeostasis, 533–534
Somatostatin analogue, 502
Somatostatin receptor ligands (SRLs)
octreotide LAR, 375
pasireotide LAR, 376
Somatotroph adenomas, 566–570
acromegaly, 118
densely and sparsely granulated, 119
eosinophilic or chromophobic, 119
GH-cell, 120
GH-secreting, 120
hyperprolactinemia, 119
immunoreactive, 120
mammosomatotroph Cell, 120
mixed GH-cell and PRL-cell, 120
signs and symptoms, 118
Sphenoid pneumatization, 488
Sphenoid sinus aeration, 488
Sphenoid sinus mucosa, 321
Sphenoid sinus pneumatization, 489
Sphenoid sinus type, 411
Sphenopalatine artery (SPA), 176, 323, 535
Spindle cell oncocytomas (SCOs), 132
Staged transcranial-transsphenoidal approach, 525
Staged transsphenoidal approach, 525
Stalk effect-related hyperprolactinemia, 459
Stereotactic radiosurgery (SRS), 542–553, 559, 560, 565
ACTH, 540
ACTH-secreting adenomas, 540
apparent radio-resistant effects, antisecreting medications, 553
complications
acute toxicity, 550
cranial neuropathy, 550–551
hypothalamic-pituitary dysfunction, 550
Late Adverse Radiation Effects, 551
risk, 550
side effects, ionizing radiation, 550
contemporary management, 554
Cushing's disease, 540
Delayed post-radiosurgical hypopituitarism, 554
devices and techniques, 540
EBRT *vs*. management of pitutiary adenomas, 551
endocrine remission rates, 540
GH-secreting adenomas, 540
GKRS, 540
histological entities
nonfunctioning adenomas, 552–553
linear accelerator-based devices, 541
Nelson's syndrome, 540
Neurological function, 554
nonfunctioning pituitary adenomas, 540
outcomes
functioning pituitary adenomas, 546–549
nonfunctioning pituitary adenomas, 544–546
pituitary adenomas, 539
pre-SRS evaluation, 542
technique and planning
Radiographic Images, 543
steep dose fall-off, 542
Stereotactic Frame Replacement, 542
Treatment Planning and Dose Selection, 543, 544
treatment options, 540
treatment strategy and patient selection, 541
Upfront Radiosurgery, 552
whole-sellar, MR indeterminate functioning adenomas, 554
Stereotactic radiotherapy (SRT), 561, 562
Stereotaxy, 560
Steroidogenesis inhibitors, 368, 369
Stomadeum, 404
Stress dose methylprednisolone, 422
Strokes, 575
Subtemporal approach, 209, 210
Supraorbital keyhole approach
ACF, 208
advantages, 208
disadvantage, 209
Supraorbital/pterional craniotomy, 521
Suprasellar region
cavernous sinus and skull base, 159, 161
cranial nerves, 159, 161
incisura, 159
vasculature, 162
Surgical factors, QOL, 601–605
in pituitary adenomas
complications, 605

endoscopic *vs.* microscopic transsphenoidal surgical approach, 602, 603
middle turbinate resection, 604
nasoseptal flaps, 603, 604
olfaction, 604, 605
perioperative quality of life alterations, 601, 602
Surgical indications by lesion
acromegaly, 49–50
craniopharyngiomas, 53
Cushing's disease, 50
cysts, 54
Infundibular/Hypothalamic Tumors, 53
meningiomas, 53
metastatic disease, 54
nonfunctioning tumors, 52
pituitary apoplexy, 52–53
prolactinomas, 48–49
reoperations, 55
sellar pituitary tumor, 45
sellar/suprasellar heterogeneous, 44
suprasellar extension of a pituitary tumor, 44
thyrotropic adenoma, 50–52
Surgical resection, Cushing's disease
adenoma, 433, 434
CSF, 434
dural incision, 433
endocrinological remission, 434
endoscopic procedures, 434
endoscopic technique, 432
fluoroscopy/intraoperative navigation tools, 432, 433
hypercortisolemic, 432
hypophysectomy, 434
microscopic approach, 432
microscopic technique, 434
MRI, 433
navigation/C-arm fluoroscopy, 432
panhypopituitarism, 434
pituitary surgery, 433
pseudocapsule, 433, 434
Syndrome of inappropriate antidiuretic hormone (SIADH), 37, 323, 329–332, 442, 449–452, 533

T
Targeted Therapy, 589–590
Temozolomide, 584, 586–588
Temozolomide mechanism of action, 584, 586
Third ventricle, 409
Three-dimensional (3D) endoscopy
advantages, 236–240
binocular vision, 234, 235
disadvantages, 239
dual-channel system, 234
"insect eye" technology, 235
skull base surgery, 233
transsphenoidal surgery, 239–242
2D endoscopes, 233
visionsense system, 236–238
Thrombocytopenia, 588
Thyroid hormone, 407
Thyrotroph adenomas
histopathology, 123
MEN1, 123
TSH-secreting adenomas, 123
Thyrotropic adenomas, 31, 50, 572
Transbasal approach, 296, 297
Transcavernous approach, 286, 288, 289, 293, 294
Transclival and transodontoid approaches, 291, 292
Transclival approach, 282, 283
Transcranial approach, 194–201, 204–206, 209, 296, 297
bifrontal approaches (*see* Bifrontal approach)
craniopharyngiomas, 192
meningiomas, 192
OZ, 201–204
pterional approaches (*see* Pterional approach)
sellar and parasellar regions, 191–193
subtemporal (*see* Subtemporal approach)
supraorbital keyhole approach, 208, 209
unilateral subfrontal, 207
Transcribriform approach, 290, 291
Transcribriform corridor, 280
Transinfundibular craniopharyngiomas, 418–419
Transinfundibular tumors, 409, 411
Transnasal approach
pituitary gland, 168
Transodontoid approach, 283, 284
Transplanum transtubercular approach, 291
Transplanum transtuberculum approach, 280–282
Transpterygoid approach, 285, 286, 292, 293
Transsellar approach, 279, 280, 289, 290
Transsphenoidal approach (TSA)
pituitary adenomas, 233
Transsphenoidal resection (TSR), 368
Transsphenoidal surgery (TSS), 390, 391, 403, 427, 441, 457
acromegaly, 385, 400
bipolar cautery, 182, 183

Transsphenoidal surgery (TSS) (*cont.*)
complications, 495–496
CSF, 183, 184, 396
Cushing's disease, 384, 399
dural incision, 181
endonasal, submucosal and trans-septal approach, 17
endoscopic and microscopic techniques, 188
endoscopy, 5, 6
GTR, 398, 399
hemostasis, 184–186
hypothalamus, 396
indications, 385
intercavernous sinuses, 181
intraoperative preparation and positioning, 387–389
intraventricular endoscopy and stereotaxy, 20
lateral visualization of parasellar lesions, 7
lumbar drain, 172–174
microsurgical trans-ethmoidal hypophysectomy, 19
morbidity and complication rate, 14
nasal-septal flap, 184
needle-tip electrocautery, 177
NFPAs, 384
nonfunctioning pituitary adenomas, 399
nonpituitary parasellar pathology, 6
OR setup, 169, 170
paranasal sinuses and pituitary gland, 15
patient positioning and preparation, 169–172
periprocedural communication and safety, 168, 169
pituitary adenoma, 383
pituitary dysfunction, 396
pneumoencephalography development, 17
postoperative care, 187
postoperative, 389
preoperative management, 386, 387
prolactinoma, 385
recurrence, 384
sella turcica, 6
sinonasal complications, 398
sphenoid sinus, 179, 180
transnasal transsphenoidal operation, 188
turbinates, 175, 176
vascular injuries, 398
videofluoroscopy, Jules Hardy, 21
visual disturbances, 397
Transtuberculum transplanum approach
craniopharyngiomas/meningiomas, 222, 223
planum sphenoidale, 222
TSH deficiency, 504
TSH-secreting pituitary tumors (TSH), 377
Tuber cinereum hamartoma, 102
Tuber cinereum hamartoma or hypothalamic hamartoma, 102
Tuberculum sellae, 406
Tumor cavity hemorrhage, 323, 324
Tumor detection, 428
Tumor Grading, 126
Tumor resection
and skull base exposure, 415–417

U
Ultrasonic Doppler probe, 447
Unilateral subfrontal, 207
Upfront Radiosurgery, 552
Urinary Catheters, 333, 334

V
Vascular endothelial growth factor (VEGF), 501, 589
Vascular injury, 323–326
arterial epistaxis, 323
bleeding, 325
carotid artery injury, 324, 325
catastrophic event, 325
Circle of Willis blood supply, 325
classification, 323
optic chiasm and pituitary infundibulum, 325, 326
sphenopalatine artery, 323
temporary hemostasis, 325
tumor cavity hemorrhage, 323, 324
Vascularized nasoseptal flap, 312
Vascularized pedicled nasoseptal mucosal flaps, 603
Vascularized reconstruction
cerebrospinal fluid leak, 306
CSF leak rates, 305
dural defect, 307
ESBS, 305
extracranial pericranial flap (EPF), 305
inferior incision, 306
Merocel tampons, 308
nasoseptal flap, 305, 306, 308
perichondrium and cartilage/bone, 307
superior incision, 306
suprasellar tumors, 308
temporoparietal fascial flap (TPFF), 305
vertical incision, 306
Vidian nerve, 322
Vision loss, 510
Visionsense 3D, 235, 239

Visionsense VSII machine, 239, 240
Visionsense VSIII machine, 238, 239
Visual field testing, 535
Visual Loss, 80
Visual pathway injury, 574
Visual symptoms, 505
Volume-acquisition T1WI contrast-enhanced MRI sequences, 411
Vomer, 447

W
Wet keratin, 404
World Health Organization (WHO), 582

X
X-linked acrogigantism (XLAG) associated with GPR101 microduplication, 114