Introduction and Methods for the Congress of Neurological Surgeons Systematic Review and Evidence-based Guidelines for the Treatment of Adults with Functioning Pituitary Adenomas (FPA)

Sponsors: Congress of Neurological Surgeons (CNS) and the AANS/CNS Section on Tumors

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ABSTRACT

Background: The management of patients with functioning pituitary adenomas (FPA) is an important facet of medicine for all physicians involved in their care.

Objective: This evidence-based guidelines aims at providing recommendations for the management of patients with FPA.

Methods: The medical literature from 1946 (inception of the database) to June 8, 2021, was searched to determine available information to create evidence-based recommendations related to endocrinological management, imaging, surgery, radiosurgery and radiotherapy of patients with FPA.

Results: The writing group utilized the information from the literature search to formulate recommendations that were evidence based and not based on consensus or expert opinion.

Conclusion: This series of guidelines documents provides evidence-based recommendations for the management of FPA patients. It sets a benchmark as to what we really know about the management of this common disease. It also provides clues to key investigations that are necessary to move forward in continuing to improve the outcomes of this patient population.

INTRODUCTION

Background and Rationale

Pituitary adenomas or pituitary neuroendocrine tumors are considered primary tumors in the pituitary gland[1]. Pituitary adenomas are the most common intracranial neoplasms. Functioning pituitary adenoma (FPA) accounts for approximately two-thirds of adenomas. Multiple disciplines are involved in managing adult patients with FPA in various clinical settings. As these patients are within a multifaceted system and approach, a clinical guideline is needed to provide treatment for these patients with appropriate information and decision-making process.

These guidelines are presented as a set of four peer-reviewed papers focusing on four cardinal elements necessary to improve outcomes for this patient population, namely endocrine management, imaging, surgery and radiation. They are produced using the evidence-based methodology supported by the Joint Guidelines Review Committee (JGRC) of the American Association of Neurological Surgeons (AANS) and Congress of Neurological Surgeons (CNS).

Objectives and Guideline Panel Development

The overall objective of this series of guidelines documents is to provide evidence-based recommendations for the management of patients with FPA centering on questions related to the most commonly used diagnostic and treatment modalities. The most important step in accomplishing this goal is a systematic review of the literature. The AANS/CNS Section on Tumors recruited representatives from neurosurgery, radiation oncology, medical endocrinology, and neuroradiology to form a multi-disciplinary clinical panel of experts (**Table 1**) who developed the evidence-based practice guidelines from the systematic review results.

The primary consequence of this work will ideally be to point out the current state of knowledge about the management of this disease process and serve as a point of reference for the development of diagnostic and treatment improvements for patients with this diagnosis.

METHODS

Topical Range of the Systematic Review and Clinical Practice Guidelines

The questions to be answered about the treatment of adult FPA to be addressed by the systematic literature review were determined by the clinical panel. These questions are presented at the beginning of each guideline section, of which there are four in all. This includes questions about endocrine management, diagnostic imaging, cytoreductive surgery, radiosurgery and radiotherapy.

Literature Examination Approach

A broad literature search strategy was undertaken to identify citations relevant to the management of FPA. The MEDLINE® and Embase® electronic databases for the period from 1946 (inception of the database) to June 8, 2021, was utilized. The search strategy used a combination of subheadings and text words. Reference lists from the publications that met inclusion criteria were also screened for potentially relevant studies.

Study Selection, Quality Assessment and Statistical Methods

The bibliographic database search identified potentially relevant citations. Two authors reviewed titles and abstracts based on the eligibility criteria defined for each section's topic. Any disagreements regarding relevance were resolved by a third author when necessary. Full-text articles of the selected abstracts were then gathered, and the same evaluation process was applied. Articles that met the eligibility criteria for one or more questions were categorized according to the specific questions they addressed, with reasons for exclusion documented. The eligibility criteria for each question are detailed in the individual clinical practice guideline papers in this series.

Publications that met the eligibility criteria had their data extracted by one reviewer, with a second reviewer verifying the information. Evidence and summary tables, which included the extracted study data and evidence classification, were created for each question. The literature in these evidence tables was further discussed in the scientific foundation of each section, highlighting key points that support the classification and recommendations.

AANS/CNS Evidence Classes and Levels of Recommendations

Both the evidence classification and the strength of therapeutic recommendations were graded using standardized AANS/CNS criteria (**Table 2**). The evidence class assigned to each study was determined by its design (i.e., class I, II, or III). The strength of the recommendations (i.e., level I, II, or III) was directly tied to the evidence classification, considering factors such as study quality and whether the study objectives were achieved, beyond just the design. Specifically, the class of evidence and the strength of a recommendation could be downgraded based on consensus input if there were concerns about the methodology of the studies used as evidence. A detailed summary of the methodology used in this evidence-based update, including the techniques for classifying data and linking it to recommendations, is available at: https://www.cns.org/guidelines/guideline-development-methodology.

Guideline Panel Consensus and Practice Guideline Approval Process

Writing groups were formed from the full clinical guideline panel, with members selected based on their expertise in the relevant disciplines and therapeutic areas included in the guidelines. Each group was responsible for literature selection, and for creating and editing the evidence/summary tables related to their specific field. The evidence tables were organized with the most recent studies listed first, followed by earlier studies in reverse chronological order.

Each table included the last author's name, journal, year, a brief study description, the assigned data class, and the study's conclusion. Authors were instructed to present the data concisely and factually to ensure clarity and understanding of each literature entry.

Each cited study in the table is discussed more extensively in the scientific foundation, with further details on the classification choices noted there. Using this information, the writing groups drafted the clinical practice guidelines for their respective disciplines. The drafts were then circulated to the entire clinical guideline panel for multidisciplinary feedback, discussion, and final approval.

Once the evidence-based clinical practice guidelines for managing progressive glioblastoma were completed, they were submitted to the JGRC for assessment of methodology, content, and conclusions. **Figure 1** outlines the key steps in the development of these clinical practice guidelines.

CONCLUSION

These guidelines were primarily developed to offer evidence-based recommendations for the treatment of patients with functioning pituitary adenomas (FPA), establishing a benchmark for future improvements in care. By designing future research to generate high-quality evidence that addresses the weaknesses and limitations identified in these guidelines, progress toward better treatment for this condition can be achieved.

Additionally, the recommendations are intended for careful consideration by practicing physicians, who must take into account the unique aspects of each patient's condition before applying them. It is important to recognize that applying published guidelines often generates strong, sometimes conflicting, opinions. These guidelines are not meant to resolve these debates, nor is it realistic to expect any guidelines to do so.

Ongoing research will continue to shape the field, and these guidelines are intended to be updated in five years, with earlier revisions possible if significant, practice-changing evidence emerges.

Disclaimer of Liability

This clinical systematic review and evidence-based guideline was developed by a physician volunteer task force as an educational tool that reflects the current state of knowledge at the time of completion. Each chapter is designed to provide an accurate review of the subject matter covered. This guideline is disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in their development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a competent physician should be sought. The proposals contained in these guidelines may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in these guidelines must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

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Conflicts of Interest

All Guideline Task Force members were required to disclose all potential COIs prior to beginning work on the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines Review Committee. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved of the nomination and participation on the task force. The CNS Guidelines Committee and Guideline Task Force Chair may approve nominations of task force members with possible conflicts and restrict the writing, reviewing, and/or voting privileges of that person to topics that are unrelated to the possible COIs. See Table 3 for a complete list of disclosures.

Acknowledgments

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References:

1. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro-oncology.* 2021;23(8):1231-1251.

Table 1. Functioning Pituitary Adenomas (FPA) guidelines panel members. This project was chaired by Isabelle M. Germano, MD, MBA and D. Ryan Ormond, MD

	Panel Member	Affiliation	City	State
1	Aghi, M	University of California San Francisco	San Francisco	CA
2	Belani, P	Icahn School of Medicine at Mount Sinai	New York	NY
3	Barkhoudarian, G	Pacific Facial Pain Center	Santa Monica	CA
4	Cifarelli, CP	West Virginia University	Morgantown	WV
5	Delman, B	Icahn School of Medicine at Mount Sinai	New York	NY
	Germano, IM	Icahn School of Medicine at Mount Sinai	New York	NY
6	Green, S	Icahn School of Medicine at Mount Sinai	New York	NY
7	Junn, J	Emory University	Atlanta	GA
8	Kerr, J	University of Colorado Anschutz Medical Campus	Aurora	CO
9	Lehrer, EJ	Mayo Clinic	Rochester	NY
10	Lillehei, K	University of Colorado Anschutz Medical Campus	Aurora	CO
	Ormond, DR	University of Colorado Anschutz Medical Campus	Aurora	CO
11	Oyesiku, N	University of North Carolina	Chapel Hill	NC
12	Post, KD	Icahn School of Medicine at Mount Sinai	New York	NY
13	Prevedello, D	Ohio State University, Wexner Medical Center	Columbus	OH
14	Recinos, PF	Cleaveland Clinic	Cleaveland	OH
15	Sheehan, JP	University of Virginia Health System	Charlottsville	VA
16	Travers, S	University of Colorado Anschutz Medical Campus	Aurora	CO
17	Zada, G	Keck Medicine at University of Southern California	Los Angeles	CA
18	Ziu, C	Inova Schar Cancer Institute	Fairfax	VA

Table 2. AANS/CNS Evidence Classes and Levels of Recommendations.

Evidence classification	
Class I	Evidence provided by one or more well-designed randomized controlled clinical trials, including overview (meta-analyses) of such trials
Class II	Evidence provided by well-designed observational studies with concurrent controls (e.g. case control and cohort studies)
Class III	Evidence provided by expert opinion, case series, case reports and studies with historical controls
Levels of recommendation	
Level I	Generally accepted principles for patient management, which reflect a high degree of clinical certainty (usually this requires Class I evidence which directly addresses the clinical questions or overwhelming Class II evidence when circumstances preclude randomized clinical trials)
Level II	Recommendations for patient management which reflect clinical certainty (usually this requires Class II evidence or a strong consensus of class III evidence)
Level III	Other strategies for patient management for which the clinical utility is uncertain (inconclusive or conflicting evidence or opinion)

Table 3. Task Force Disclosures

Author	COI
Manish Aghi, MD, PhD, MAS	Telix Pharmaceuticals
Garni Barkhoudarian, MD	Medexus Pharma, Inc.; Karl Storz Endoscopy-America; Zimmer Biomet Holdings; Integra Life Science Corporation; Merz Pharmaceticals LLC
Puneet Belani, MD	Penumbra, Inc.
Christopher P Cifarelli	Omniscient Neurotechnology America Ltd
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Jacqueline Junn, MD	None
Janice KerrMD	None
Eric J. Lehrer, MD	Novocure Inc.
Kevin Lillehei, MD	DePuy Synthes Sales Inc.
D. Ryan Ormond, MD, PhD	Longeviti Neuro Solutions LLC; DePuy Synthes Sales Inc.
Nelson Oyesiku, MD, PhD, FACS	None
Kalmon D Post, MD	None
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Sarah Travers, MD	Globus Medical, Inc., Medtronic, Inc. ZIMVIE INC., Olympus America Inc., Baxter Healthcare
Christie Turin More, MD	Amryt Pharma Holdings Ltd
Gabriel Zada, MD	Stryker Corporation
Mateo Ziu, MD	Omniscient Neurotechnology America Ltd, GT Medical Technologies, Inc

Figure 1. Overview of the Functioning Pituitary Adenoma guidelines