Congress of Neurological Surgeons Systematic Review and Evidence-Based Guideline on Primary Management of Patients With Nonfunctioning Pituitary Adenomas

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BACKGROUND: Nonfunctioning pituitary adenomas (NFPAs) are among the most common pituitary lesions and may present clinically with vision loss and hypopituitarism.
OBJECTIVE: To characterize the existing literature as it pertains to the initial management of NFPAs.
METHODS: A systematic literature review was conducted to identify and screen articles assessing primary treatment options (surgical, medical, radiation based, or observation) for NFPAs. Outcomes assessed included vision-, endocrine-, and headache-related symptoms, as well as tumor response to therapy. Twenty-five studies met inclusion criteria for analysis.
RESULTS: A considerable amount of class II evidence (14 studies) was identified supporting primary surgical intervention in patients with symptomatic NFPA macroadenomas, resulting in immediate tumor volume reduction in nearly all patients and a residual tumor rate of 10% to 36%. One prospective, observational cohort study and multiple retrospective studies showed improved visual function in 75% to 91% of surgically treated patients and improved hypopituitarism in 35% to 50% of patients. Limited class II evidence showed inconsistent benefits for observation alone (1 study), primary radiation-based treatment (3 studies), or primary medical treatment (8 studies) for improving vision, headaches, hypopituitarism, or tumor volume. One retrospective study implementing observation alone showed tumor progression in 50% of patients and a requirement for surgery in 21% of patients. Eight studies assessing primary medical therapy for NFPAs showed inconsistent tumor response rates using somatostatin analogs (12%-40% response rate), dopamine agonist therapy (0%-61% response rate), or combination therapy (60% response rate). Three studies reporting primary radiosurgery for NFPAs showed decreased tumor size in 38% to 60% of patients.
CONCLUSION: Multiple retrospective and some prospective studies have demonstrated consistent effectiveness of primary surgical resection of symptomatic NFPAs with acceptable morbidity rates. Limited and inconsistent reports are available for alternative treatment strategies, including radiation, medical treatment, and observation alone; these modalities may, however, play a valid role in patients who are not surgical candidates. Based on the available evidence, the authors recommend surgical resection as the preferred primary intervention for symptomatic NFPAs. The full guidelines document for this chapter can be located at https://www.cns.org/guidelines/guidelines-management-patients-nonfunctioning-pituitary-adenomas/Chapter_5.

KEY WORDS: Initial, Observation, Nonfunctioning pituitary adenoma, Treatment, Surgery

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Nonfunctioning pituitary adenomas (NFPAs) are among the most common pituitary lesions and may present clinically with vision loss and hypopituitarism, among other symptoms. Options for primary treatment of NFPAs include surgical resection, radiation therapy, medical management, and observation. A systematic literature review was conducted to identify and screen articles assessing

ABBREVIATION: NFPA, nonfunctioning pituitary adenoma

these primary treatment options (surgery, radiation, medical, or observation) for NFPAs. Outcomes assessed included vision-, endocrine-, and headache-related symptoms, as well as tumor response to therapy.

METHODS

The guideline task force members conducted a systematic review of the literature relevant to the management of NFPAs. Additional details of the systematic review are provided online and within the introduction and methodology chapter of the guideline (https://www.cns.org/guidelines/guidelines-management-patients-non-functioning-pituitary-adenomas/Chapter_5). The task force collaborated with a medical librarian to search for articles published from January 1, 1966, to October 1, 2014. Two electronic databases, PubMed and the Cochrane Central Register of Controlled Trials, were searched. Strategies for searching the electronic databases were constructed by the task force members and the medical librarian using previously published search strategies to identify relevant studies.

RESULTS

Twenty-six studies met inclusion criteria for analysis, of which all were class III observational studies. No class I evidence comparing any treatment modality was available. A large amount of class III evidence supporting the use of surgical intervention as the primary treatment method for NFPAs exists in the literature. Fourteen studies were identified supporting primary surgical intervention in patients with symptomatic nonfunctioning pituitary macroadenomas, resulting in immediate tumor volume reduction in nearly all patients and a residual tumor rate of 10% to 36%. One prospective, observational cohort study and multiple retrospective studies showed improved visual function in 75% to 91% of surgically treated patients and improved hypopituitarism in 35% to 50% of patients.[1-10] The complication rates of surgical intervention have also been demonstrated to be low. A large series of patients who underwent surgery for symptomatic NFPAs described a total complication rate of 7.1%, with the most common complications including cerebrospinal fluid leak (4.7%), meningitis (2.0%), and vision deterioration (2.0%).[11]

Based on this evidence, the following recommendation can be made: **Surgical resection is recommended as the primary treatment of symptomatic patients with NFPAs (level III recommendation)**. Limited class III evidence showed inconsistent benefits for observation alone (2 studies), primary radiation-based treatment (3 studies), or primary medical treatment (8 studies) for improving vision, headaches, hypopituitarism, or tumor volume for symptomatic NFPAs. There was insufficient evidence to make a recommendation regarding the primary treatment strategy for asymptomatic lesions.

Natural history studies implementing only observation of NFPAs have rarely been reported in the literature. Two studies reporting observation alone showed tumor progression in 40% to 50% of patients and a requirement for surgery in 21% to 28.5% of patients.[12,13] The limited studies available on observation alone for symptomatic NFPAs do not support this strategy for the primary treatment of these lesions.

Studies of radiation therapy as a primary treatment method have not shown superiority or equivalence to surgical resection of NFPAs. Radiation therapy has been shown to be an effective secondary treatment modality when used as an adjunct to surgical resection in cases of postoperative residual tumor or recurrence. Radiation therapy may also have a role in the primary management of patients who are unfit for surgical intervention based on severe medical comorbidities or preoperative functional status. Assessment of the efficacy of radiation therapy in the primary treatment of NFPAs is sparse. Three studies reporting primary radiosurgery for NFPAs showed decreased tumor size in 38% to 60% of patients.[14-16] More recent developments in radiation therapy, including non-fractionated gamma knife radiosurgery, have led to alternative treatment options for NFPAs; however, these newer technologies currently have limited evidence to support their use as a primary treatment strategy.

Evidence supporting consistent effective treatment of NFPAs with medical therapy alone is also sparse and inconsistent. Despite their inherent lack of hormonal functionality, the primary medical agents that have been assessed in NFPAs are dopamine agonist and somatostatin analog agents. Several studies have also investigated the role of medical management of NFPAs using various endocrinologic analogs in combination. Eight studies assessing primary medical therapy for NFPAs showed inconsistent tumor response rates using somatostatin analogs (12%-40% response rate), dopamine agonist therapy (0%-61% response rate), or combination therapy (60% response rate).[17-24] Attempts have also been made to characterize the receptors for certain molecules present on NFPAs and differentiating the response to different medical therapies targeting these receptors. Neither the use of dopamine agonists nor somatostatin analogs, whether alone or in combination, has been shown to have a significant and consistent therapeutic effect on these tumors.

CONCLUSION

Based on the available evidence, surgical management is the preferred method of primary treatment of symptomatic NFPAs in patients with symptoms of visual field deficit or vison loss, ophthalmoplegia, compression of the optic apparatus on magnetic resonance imaging, endocrine dysfunction, including hypopituitarism or stalk effect causing hyperprolactinemia, pituitary apoplexy, refractory headaches not attributable to other headache syndromes, or other neurologic deficits related to compression from the tumor, when compared with radiation, medical therapies, or observation alone as primary treatment strategies. Limited and inconsistent reports are available for alternative treatment strategies, including radiation, medical treatment, or observation alone; these modalities may, however, play a valid role in patients who are not surgical candidates.

Disclosures

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Disclaimer of Liability

This clinical systematic review and evidence-based guideline were developed by a physician volunteer task force as an educational tool that reflects the current state of knowledge at the time of completion. The presentations are 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 on its 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 physician should be sought. The recommendations contained in this guideline may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in this guideline 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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