Imaging of Resected Nonfunctioning Pituitary Adenomas: The Cost of Surveillance

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Abstract

Objectives To determine the cost of annual magnetic resonance imaging (MRI) surveillance after resection of nonfunctioning pituitary adenomas (NFPAs) and its effectiveness in reducing visual compromise due to tumor recurrence.

Design Retrospective case series.

Setting Vanderbilt University Medical Center (2003–2011).

Participants A total of 120 patients underwent primary transsphenoidal resection and surveillance of NFPAs between 2003 and 2011.

Main Outcome Measures Time from initial surgery to most recent imaging or progression. Surveillance MRI costs according to Centers for Medicare and Medicaid database and visual field deficits.

Results Patients received 382 surveillance scans at a total cost of \$218,477.30. The median follow-up was 47 months (interquartile range [IQR]: 26–76), and the median interval between scans was 357 days (IQR: 225–434). Overall, 50 scans (13%) revealed tumor growth. The cost per scan revealing growth was \$4,369.55. The cost to identify 19 patients (16%) with clinically significant growth was \$11,498.80 per patient. A total of 5 of 19 patients (26%) experienced new visual deficits prior to intervention. Patients with visual decline tended to have longer scan intervals than those with preserved vision (mean: 239 versus 794 days; $p = 0.0584$). No patient with annual surveillance imaging experienced visual decline.

Conclusions Annual MRI scans are a sensitive and cost-conscious method to identify NFPA recurrence prior to visual decline.

Keywords

- pituitary adenoma
- follow-up
- management
- cost
- MRI

Introduction

Nonfunctioning pituitary adenomas (NFPAs) comprise approximately a third of all pituitary tumors.¹ They are second only to prolactinomas in frequency.² As their name implies, NFPAs lack endocrine activity to precipitate earlier symptom

onset and therefore are typically large macroadenomas at presentation. As a result, the most common clinical signs at presentation are due to mass effect on the surrounding structures and include vision loss, hormone deficiencies, or headache.

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The primary indication for surgical decompression is to reverse or prevent visual deficit, and endoscopic endonasal transsphenoidal surgery is considered the first-line therapy. NFPAs carry the lowest remission rate (44%) of any subtype. Many tumor recurrences occur in the first 5 years after resection, yet the frequency of remote recurrence even 10 years after initial resection is significant and cannot be overlooked.^{1,3,4} Progression-free survival rates at 5, 10, and 15 years have been reported to be 91%, 81%, and 69%, respectively.⁴ In addition to surgical resection, adjuvant stereotactic or fractional external-beam radiation may be indicated for recurrence or significant postoperative tumor residual despite repeat resections. However, postoperative irradiation carries significant risks; hypopituitarism, which occurs in up to 40 to 50% of cases, visual compromise, which occurs in up to 3 to 4% of cases, and impaired quality of life.^{5,6} Thus regular long-term follow-up is recommended over routine postoperative radiation.

Monitoring for recurrence is uniquely complex in nonfunctioning tumors due to the lack of appropriate biochemical surveillance, the subjectivity of radiography, and the need for long-term follow up.²⁻⁴ Multiple predictive factors for recurrence have been proposed. Subtotal resection, cavernous sinus invasion, younger age, larger tumor size, and aggressive histologic features have all been proposed as potential risk factors for recurrence; however, supporting data have been mixed, and no definite predictors have been identified.^{3,7-14} Due to lack of alternatives, current recommendations state that annual magnetic resonance imaging (MRI) along with annual or semiannual visual field examinations is the standard of care for follow-up.¹⁵ Although MRI is 99% sensitive, it is nonspecific (29%) for pituitary lesions and is capital intensive for the patient and health care system as a whole.¹⁶ Given the increasing effort to reduce health care costs, we sought to quantify the cost as well as determine the benefit of annual imaging surveillance and any risks associated with prolonged scan intervals. Furthermore, we sought to determine the effect of demographic or socioeconomic factors on patient compliance with follow-up recommendations.

Methods

We conducted a retrospective analysis of all patients with a primary pathologic diagnosis of NFPA who underwent surgical resection at the Vanderbilt University Medical Center (VUMC) between 2003 and 2011. Two neurosurgeons resected 168 NFPAs during this time period, and pathology was confirmed by a neuropathologist. All operations were completed via a transsphenoidal approach in collaboration with a rhinologist. Microscopic or endoscopic techniques were used according to surgeon preference. Exclusion criteria were as follows: children < 18 years of age, history of prior pituitary intervention, history of craniotomy, silent corticotrophic tumors, multiple endocrine neoplasia syndrome, and inability to obtain MRIs. A total of 143 patients met the inclusion criteria. After review of the records, an additional 23 patients were excluded because they did not receive imaging after

their initial postoperative MRI. A total of 120 patients remained in the final analysis.

The demographics, clinical course, operative reports, radiation history, pathology, visual fields, and MRI imaging were reviewed and entered into a REDCap database.¹⁷ Recorded demographic and socioeconomic variables included age, race, gender, marital status, level of education, insurance status, employment, and distance of travel from home to VUMC. Length of surveillance was calculated as the time from the date of surgery to the most recent MRI scan or date of the scan that led to an intervention. We examined surveillance after primary intervention only. Each surveillance scan was treated as an independent event that monitored for recurrence. The scan interval was defined as time from intervention or previous scan to current scan.

All information was deidentified prior to statistical analysis in Microsoft Excel and JMP Pro.^{18,19} Descriptive statistics were reported as means and standard deviations for normally distributed variables and medians with interquartile ranges (IQRs) for nonnormal distributions. Pearson chi-square analysis was performed to identify any differences between categorical variables. The Fisher exact test was utilized when one category had five or fewer patients. One-way analysis of variance (ANOVA) was used to compare differences in MRI scan intervals between groups. Welch ANOVA was used in cases of unequal variance (Brown-Forsythe < 0.05). Kaplan-Meier survival analysis was performed to estimate progression-free survival. Univariate Cox proportional hazard analyses were then conducted to identify demographic, radiographic, and treatment variables associated with recurrence. Cost calculations were performed using the Centers for Medicare and Medicaid 2013 reimbursement for a MRI with and without contrast, which totaled \$571.93.²⁰

Results

Presentation and Patient Characteristics

Of the 120 patients included in the final analysis, 57 were male and 63 were female with a median age of 55 years at diagnosis. On initial presentation, 85 patients (71%) had an endocrine abnormality, 74 patients (62%) had headache, and 53 patients (44%) had a visual field deficit. The tumor was an incidental finding in 44 patients (37%). The median tumor diameter was 24.1 mm (range: 11–60 mm). A total of 101 tumors (84%) exhibited suprasellar extension, 87 (72%) had chiasmal compression, and 56 (47%) had extension into at least one cavernous sinus on preoperative MRI (→ **Table 1**).

According to center protocol, postoperative MRI scans were obtained on patients 6 weeks postoperatively. These revealed a gross total resection in 27 patients (23%). Seventy-five (62%) underwent subtotal resection. Another 18 patients (15%) had imaging that was considered inconclusive revealing either scant residual tumor or postoperative debris. There was no significant difference in preoperative radiologic characteristics or extent of resection outcomes between the microscopic and endoscopic approaches. Ten patients (8%) were treated with adjunctive radiation in addition to surgical

Table 1 Preoperative patient variables and tumor characteristics

	Total (n = 120)	Recurrence (n = 37)	Stable (n = 83)	p value
Age at resection, y				
Mean ± SD	54.3 ± 13.0	54.6 ± 12.6	54.1 ± 13.2	0.480
Gender (%)				
Male	63 (53)	13 (35)	44(53)	0.325
Female	57 (47)	24 (65)	39 (47)	
Visual field deficit (%)				
Yes	53 (44)	16 (43)	37 (45)	0.339
No	67 (56)	21 (57)	46 (55)	
Endocrine abnormality (%)				
Yes	85 (71)	26 (70)	59 (71)	0.712
No	35 (29)	11 (30)	24 (29)	
Headache (%)				
Yes	74 (62)	18 (49)	56 (67)	0.060
No	46 (38)	19 (51)	27 (33)	
Incidental finding (%)				
Yes	44 (37)	13 (35)	31 (37)	0.555
No	76 (63)	24 (65)	52 (63)	
Cavernous sinus invasion (%)				
Yes	56 (47)	18 (49)	37 (46)	0.168
No	64 (53)	19 (51)	46 (55)	
Suprasellar extension (%)				
Yes	101 (84)	30 (81)	71 (86)	0.979
No	19 (16)	7 (19)	12 (14)	
Hemorrhage (%)				
Yes	15 (13)	4 (11)	11 (13)	0.911
No	105 (87)	33 (89)	72 (87)	
Chiasm compression (%)				
Yes	87 (72)	27 (73)	60 (72)	0.322
No	33 (28)	10 (27)	23 (28)	
Largest dimension, mm				
Mean ± SD	24.1 ± 8.9	24.6 ± 8.6	23.8 ± 9.1	0.535

Abbreviation: SD, standard deviation.

resection due to the presence of significant unresectable residual disease (►Table 2).

Surveillance and Recurrence

Postoperative imaging was available for patients for a median duration of 47 months (IQR: 26–76). Patients received between 1 and 11 surveillance MRI scans following their routine postoperative imaging during that time. The overall median interval between scans was 357 days (IQR: 226–434) (►Table 2). Thirty-seven patients (31%) experienced recurrence or regrowth of residual tumor during the surveillance period. Progression-free survival was 95% at 1 year, 90% at 2 years, and 58% at 5 years (►Fig. 1). There were no significant differences in demographics, operative, or radiographic variables between those patients who experienced a recurrence and those who did not. No patient treated with adjunctive radiation had evidence of recurrence, which was statistically

significant when compared with recurrence without radiation treatment ($p = 0.0005$) (►Table 2). Notably, the MRI scanning intervals demonstrating tumor recurrence were significantly longer than those revealing stable tumors (529 versus 350 days; $F = 0.0051$). Additionally, patients who experienced a recurrence had a longer median length of follow-up (72 versus 39 months), but this did not have a statistically significant effect on recurrence ($p = 0.425$). Follow-up duration was not associated with age, gender, race, marital status, level of education, travel distance to hospital, employment, or insurance status.

Cost Calculations

The 120 patients received a total of 382 surveillance MRI scans bringing the total cost of surveillance to \$218,477.30 using the CMS 2013 reimbursement value. Fifty (13%) of these scans identified a regrowth or recurrence. The cost to detect a

Table 2 Relationship between treatment and surveillance variables and recurrence

	Total	Recurrence (n = 37)	Stable (n = 83)	p value
Extent of resection (%)				
GTR	27 (23)	4 (11)	20 (24)	0.112 ^a
STR	75 (62)	26 (70)	49 (59)	
Indeterminate	18 (15)	7 (19)	14 (17)	
Adjuvantive radiation (%)				
Yes	10 (8)	0 (0)	10 (12)	0.0005 ^a
No	110 (92)	37 (100)	73 (87)	
Length of follow up, mo				
Median (IQR)	47 (26–76)	72 (52–88)	39 (21–70)	0.425 ^a
MRI interval, d ^c				
Median (IQR)	356 (226–435)	529 (261–741)	350 (225–408)	0.0051 ^b
Progression-free survival, % ^d				
1 y	95			
2 y	90			
5 y	58			

Abbreviations: GTR, gross total resection; IQR, interquartile range; MRI, magnetic resonance imaging; STR, subtotal resection.

^aCox proportional hazards analysis.

^bWelch analysis of variance.

^cCalculations based on intervals between all MRIs revealing either primary recurrence or stable disease.

^dKaplan-Meier estimate.

change was therefore \$4,369.55. Of the 50 scans that identified a change, 19 (38%) led to a change in management (15 repeat surgery and 4 radiation therapy). The cost for each of these clinically significant changes was \$11,490.80 (► Fig. 2). Patients who had progression but did not require treatment continued with MRI surveillance.

Visual Decline

No patients who received scans at the recommended yearly intervals developed a visual deficit. Five of the 19 patients (26%) who eventually required a second intervention experienced a change in their visual fields prior to treatment (► Fig. 3). In fact, all five (100%) of the patients who lost vision were not compliant with the recommended annual

MRI scanning interval, which was statistically significant when compared with patients with preserved vision at the time of repeat intervention ($p = 0.009$). Additionally, scan intervals before intervention tended to be longer in patients with visual loss than in patients who underwent a second procedure with preserved vision (mean: 239 versus 794 days; $p = 0.0584$). Three of these five patients had improvement in their vision following intervention.

Discussion

The purpose of this study was to make a cost-conscious recommendation regarding follow-up imaging intervals of surgically resected NFPAs for adult patients. Current recommendations for routine surveillance of NFPAs are based on the desire to preserve visual function. In general, patients with visual impairment have high indirect costs due to productivity loss, higher direct health care expenditures, and lower quality of life.^{21,22} The results presented here reveal that although annual imaging is financially burdensome, it prevents patients from paying the price of visual loss. All patients in our sample who followed the recommendations had preservation of their vision including cases of tumor recurrence. Additionally, the intervals between scan acquisition in the group that had clinically significant tumor growth and visual decline were longer than the group that required clinical intervention but did not experience visual decline. Taken together, these data suggest that annual imaging is appropriate interval surveillance in these patients.

It may be suggested that formal visual field testing could serve as a cost-saving strategy to monitor for tumor

Fig. 1 Kaplan-Meier curve of progression-free survival after resection of a nonfunctioning pituitary adenoma.

Fig. 2 Diagram of patient flow and cost calculations to detect a clinically significant tumor recurrence. XRT, external-beam radiation therapy.

recurrence. However, visual field testing has not been demonstrated to prevent visual decline and can necessitate an urgent intervention once detected.²³ Additionally, our data support conclusions from prior studies that demonstrated that tumor growth often occurs without immediate visual compromise.^{23,24} Although worsening or new-onset visual field deficit is one of the primary indicators for surgical reintervention, isolated visual field testing does not identify tumor growth until there is critical compression of the optic apparatus. Because the goal of surgical management is to relieve and prevent future mass effect, monitoring for neurologic sequelae of tumor growth is not an appropriate form of follow-up care. Based on the results of this study and prior results in the literature, annual MRI follow-up is strongly recommended, and visual field monitoring may be a useful adjunct.¹⁵

According to the current standard of care for postoperative pituitary follow-up, the cost associated with detecting clinically significant growth in this population was \$11,490.80. Because the calculations were based on CMS reimbursement,²⁰ this is likely an underestimate of actual cost. The actual cost of an MRI varies by insurance provider and region

of the country, and data from one individual or one institution are not generalizable to the greater population. Therefore, we deemed it prudent to use a national standardized measure to improve the external validity of our study.

To determine the cost effectiveness of MRI surveillance, the monetary cost of regular imaging follow-up must be weighed against the cost of nondetection in terms of quality of life (QOL) in this patient population. Most reports of QOL in patients following transsphenoidal resection of NFPA have found it to be similar to normal controls, but data are lacking in the subset who experience visual compromise.^{6,25,26} The ophthalmology literature reports a loss of 0.05 quality-adjusted life-years (QALYs) for visual impairment.²¹ If one applies the conventional cost effectiveness threshold of \$50,000 per QALY, annual imaging does not appear to be cost effective to prevent mild visual impairment. However, the \$50,000 standard is somewhat arbitrary and does not reflect the public's willingness to pay, which tends to be higher for more life-altering conditions.²⁷ No studies specifically address the financial cost of visual decline in NFPA, but again, we can extrapolate from ophthalmology literature that visual deficits cause a decrease in work productivity, lower

Fig. 3 Interval immediately prior to magnetic resonance imaging revealing growth or recurrence in those patients with a clinically significant recurrence.

income, and an increase in utilization of medical care and assistive devices that come at a considerable cost to the individual and society. Frick et al reported a difference in annual income of \$8,987 between persons with visual impairment and those with normal vision. Furthermore, visual impairment led to excess annual health care expenditures totaling \$3,105.²¹ Taken together, the average cost of detecting growth (\$11,490.80) is offset in 1 year of living with a visual impairment (\$12,092). This cost is even greater if the patient is blind. In the face of current imprecise cost-effectiveness standards in the case of NFPA, we believe the cost of annual imaging is prudent and justified given the cost of potential complications. However, formal cost effectiveness and QOL research is necessary in this area to make more definitive recommendations.

Our work is limited by the retrospective nature of data collection and the inherent flaws of this design. We restricted our sample to patients treated in the era of the electronic medical record with surgical treatment exclusively at our tertiary care institution. This reduced variability within our data but may have introduced selection bias. Thus this study should be repeated by other institutions to test external validity.

An additional inherent limitation to this study is the length of follow-up. Previous studies have revealed that NFPA can occur > 10 years after resection,^{1,3} yet our median follow-up was only 47 months. Accordingly, fewer total MRI scans were performed on our sample than are recommended by the current guidelines. This lowered the overall cost of surveillance scans. Even so, the recurrence rate in this cohort (31%) was in the range of that reported in previous studies.^{14,28} Presumably, longer follow-up would correspond to more MRIs and thereby a higher cost to detect clinically significant change but also to a higher rate of detected recurrences as predicted by the Kaplan-Meier curve. Without long-term data from a large population, we are unable to assess the length of time for which annual MRI scans may be cost effective. However, the current data reflects the reality of practice in which not every patient follows the recommended guidelines and is therefore a reasonable and generalizable cost estimate.

Several potential barriers to care may account for inconsistent patient follow-up in our sample. First is the issue of cost. The out-of-pocket cost for a brain MRI varies greatly depending on a patient's insurance deductible, hospital location, and the insurance company's individual agreement with that hospital. This may or may not be deemed affordable to the patient depending on their financial situation and degree of concern about potential tumor recurrence. Level of concern often depends on patient education and understanding of their long-term risk of recurrence. For example, patients who are initially concerned enough to faithfully obtain their annual MRIs may be lulled into a false sense of security after the first two or three stable scans and choose to discontinue follow-up.

Furthermore, travel to the appointment can be an additional barrier to care, especially at tertiary care institutions. The use of designated experienced surgeons at pituitary centers has been demonstrated to improve outcomes and

reduce recurrence.^{29,30} Notably, two pituitary surgeons performed all the cases reported here. However, obtaining specialized care at a pituitary center resulted in many patients in this cohort traveling hundreds of miles to come to their office visits. The travel, as well as time off from work for the patient and family members, adds an additional financial burden. Socioeconomic factors are often cited as the principal impediments to appointment attendance across many specialties.^{31–33} Our initial review of socioeconomic factors did not reveal any predictors of follow-up length or compliance. However, data on employment, education, and insurance status were difficult to verify in a retrospective manner and are not static throughout the study period. Therefore, we believe our results lack statistical power to draw firm conclusions in this regard. Detailed prospective studies are necessary to identify and address the nuanced reasons why patients discontinue follow-up after resection of a NFPA.

Imaging follow-up after NFPA resection is a necessary health care service with poor long-term compliance. The results of this study demonstrate that additional work must be done to improve patient education on the high risk for remote recurrence. In one cardiology meta-analysis of 90 studies, barriers to care were effectively overcome using reminder telephone calls, personalizing treatments, and physician encouragement as opposed to that of a midlevel provider.³⁴ Analogous strategies to address poor patient compliance should be identified and addressed in NFPA. Moreover, we must explore creative ways in which the overall cost may be decreased or offset in patients who may not be able to afford their care.

Conclusions

Annual MRI scans following resection of NFPA are a sensitive and cost-conscious way to identify tumor growth before visual decline. Vision was preserved despite tumor recurrence in all patients who followed these recommendations. Although an MRI of the brain is an expensive test, this price is outweighed by the high cost of visual impairment to the individual and society. Ultimately, prospectively collected long-term data about the natural history of this disease process is warranted because it will help guide recommendations and reduce costs.

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