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ORIGINAL ARTICLE - PITUITARIES

Defining the timing and role of acute postoperative imaging in pituitary adenoma surgery: clinical study

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Abstract

Background The ideal timing of postoperative imaging after pituitary adenoma surgery has yet to be determined. We reviewed our pituitary database to determine whether timing of routine postoperative imaging has significantly changed patients' clinical course or outcomes.

Methods Retrospective chart review of patients undergoing resection of pituitary adenoma at our university center between 2012 and 2017 was performed. Timing and indication for postoperative imaging, findings of immediate and delayed postoperative imaging, as well as re-operations and radiosurgery details were recorded. Visual functions such as acuity and visual fields were used as clinical outcome indicators. Statistical analysis was run using Microsoft Excel.

Results Five hundred and nineteen patients were identified; 443 had imaging data in our system and were included in the study. Early (< 90 days) MRIs were obtained in 71 patients and late (≥ 90 days) in 372 patients. We found statistical differences in our demographic groups including larger tumors in the early MRI group (early mean 12.33 cm^3, late mean 4.64 cm^3, $p < 0.001$) and higher Knosp grade ($p = 0.0006$). We found a significant difference in rates of return to the OR (16.9% in the early group and 4.84% in the late group; $p < 0.001$). There was a significant difference in the rate of residual identified on first postoperative MRI: 52.11% in the early group and 29.57% in the late group ($p < 0.001$). There was no difference in visual outcomes between the patient cohorts.

Conclusion After surgical treatment of pituitary adenoma, MRI obtained before 3 months is associated with higher rates of return to OR but no difference in long-term clinical outcomes. Due to cost efficiency, we argue for a delayed first postoperative MRI. The timing of MRI should also be governed by other factors such as large pituitary macroadenomas or postoperative complications. We recommend a consistent institutional protocol for determining the most cost-effective follow-up of postoperative pituitary patients.

Keywords Pituitary adenoma · MRI · Imaging · Postoperative care

Introduction

Postoperative timing of MRI following pituitary adenoma surgery is still controversial. Follow-up of asymptomatic residual tumor typically comprises observation with serial imaging and endocrinological monitoring if necessary. Repeat resection or radiation can be used for clinical or radiographic progression of residual tumor. Delaying imaging for several months is a common practice for more accurate visualization of residual tumor. Early evaluation is often difficult in the setting of acute postoperative changes including hemorrhage, packing, and undescended residual tumor in some cases [2]. However, recent literature has shown the ability of current high-definition sequences to accurately identify residual tumor on early postoperative MRI [9].

The Choosing Wisely campaign highlights the problem of unnecessary tests and procedures in the healthcare system [7]. It calls upon leading medical specialty societies and other organizations to identify tests or procedures commonly used

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in their field, in which necessity should be questioned and discussed with patients.

Current estimates of average costs associated with pituitary surgery range from $34,943.13 [1] to $76,228 [8]. A low hanging area of intervention for physicians is culling unnecessary expensive testing. One of the potential areas for improvement is early postoperative imaging after pituitary adenoma resection.

In this study, we sought to redefine the role and necessity of acute postoperative imaging after pituitary adenoma surgery. We reviewed our pituitary database to determine whether acute routine postoperative imaging has significantly changed patients' clinical course or outcomes.

Methods

Approval was obtained from the State Multiple Institutional Review Board (COMIRB Protocol 17-2116). A retrospective chart review of all patients undergoing resection of pituitary adenoma at our institution between 2012 and 2017 was performed. Demographic data, preoperative symptoms, resection technique, timing and indication for postoperative imaging, and findings of immediate and delayed postoperative imaging, as well as re-operations and radiosurgery details were recorded for each patient. Imaging results from brain MRI with and without contrast were recorded. Intraoperative MRI was not a part of our practice model for pituitary tumors at any point and was not included in our analysis. Tumor volume was estimated by the ABC/2 formula. When residual tumor was interpreted as "possible," this was counted as a positive result. Visual acuity and visual fields were used as clinical outcome indicators for all patients. They were classified as improved, worsened, or stable from preoperative baseline. Time to return to surgery or radiosurgery was also recorded. Hormonal outcomes were recorded when they resulted in return to the OR; they were not used as outcome measures as they did not apply to all patients.

Postoperative imaging was classified as either early (obtained in less than 90 days) or late (obtained at or after 90 days). The acquisition of an early postoperative scan in asymptomatic patients was part of a previous practice pattern at our hospital in which patients underwent immediate and 3-month MRI. That changed later to only delayed 3-month MRI as a new policy by the Pituitary Program. Due to this change in practice pattern, we used 90 days as the cutoff for "early" MRI before 90 days and "late" MRI after 90 days since all patients would receive 3-month or later MRI according to these protocols. Patients who did not have imaging in our system for either MRI were excluded. The most common MR sequences were an MR pituitary protocol as per our institution's current practice for outpatient follow-up, but some patients received MR brain with and without contrast in the immediate postoperative period or if their scans were performed at an outside facility.

Cost data

Costs were obtained from our Institution Financial Office Charge Department for the fiscal year 2019–2020. Costs were estimated at self-pay pricing.

Statistical analysis

Analysis was run using Microsoft Excel with Student's *t* test. $p < 0.05$ was considered significant. A multivariate analysis was performed with input variables of tumor size, age, gender, Knosp grade, pathology, new or recurrent, surgical approach, residual on postop scan and outcome variables of return to OR–rate between groups, return to OR–time, radiosurgery–rate between groups, postoperative visual acuity–final follow-up, postoperative EOM–final follow-up, and postoperative visual fields–final follow-up. To evaluate linear and logistic regression models of volume, the dataset was divide in to tertiles with cutoffs of < 1 cm^3 ($N = 109$), 1–5 cm^3 ($N = 168$), and > 5 cm^3 ($N = 116$), as well as a category for missing data.

Results

Demographic data

Upon review of our surgical database, 519 patients undergoing surgery for pituitary pathology were identified. Four hundred and forty-three of these had imaging data available in our system. Patients were classified into groups as early (obtained MRI < 90 days postoperatively) or late (obtained MRI at or after 90 days postoperatively). The early group consisted of 71 patients, and the late group had 372 patients (Fig. 1). Demographics recorded, including age, sex, tumor volume, Knosp grade, initial or recurrent, surgical approach, pathology, and time to last follow-up, are summarized in Table 1, along with statistical significance. There was a significant difference between groups in tumor size, with the early group having larger tumors (early mean 12.33 cm^3, late mean 4.64 cm^3, $p < 0.001$), higher Knosp grade ($p = 0.0006$), and a larger percentage of endoscopic (endoscopic endonasal in 56% of early patients, 11% of late patients, microscopic endonasal in 39% of early, 89% of late, and open in 4.2% of early patients and 0% of late patients).

Clinical outcomes

Clinical outcomes data for return to OR including time and indication, radiosurgery, identification of residual, and final

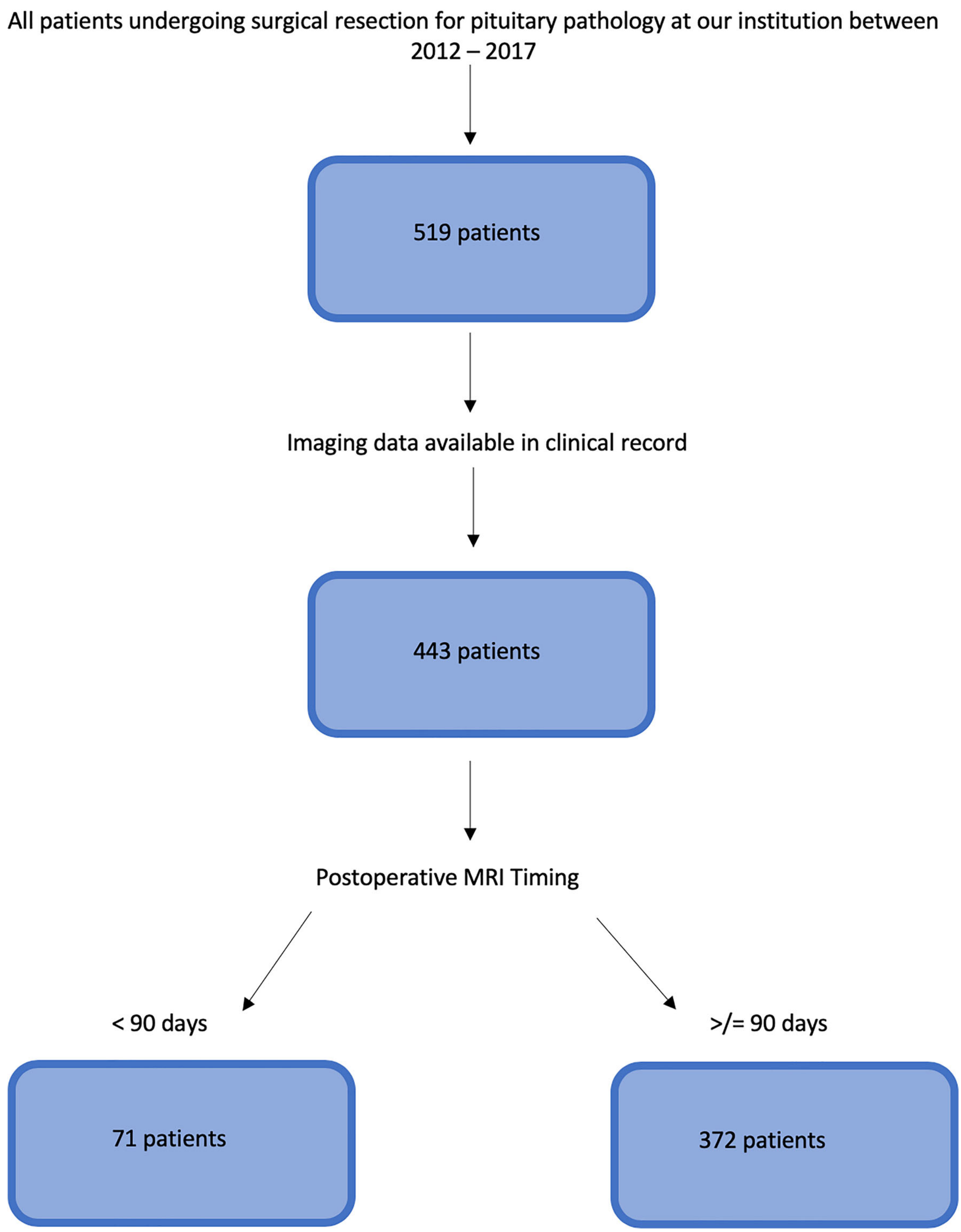

Fig. 1 Determination of clinical cohorts for study

visual acuity, visual fields, and extra-ocular movements testing are identified in Table 2. There was a significant difference in rates of return to the OR 16.9% (12/71) in the early group and 4.84% (18/372) in the late group ($p < 0.001$). The reasons for return to the OR are detailed in Table 3 and Fig. 2. There was a significant difference in the rate of residual identified on first postoperative MRI: 52.11% in the early group and 29.57% in the late group ($p < 0.001$). Of note, of the 37 patients identified to have residual on their immediate postoperative MRI, when this was repeated at 3 months postoperatively, 5 of these scans were subsequently read as negative (13.5%). Radiosurgery was performed in 0% of the early group and 2.42% of the late group ($p = 0.366$). There was no significant difference in visual outcomes between the

Table 1 Demographics recorded included age, sex, tumor volume, Knosp score, initial or recurrent, surgical approach, pathology, and time to last follow-up that are summarized along with statistical significance. In all cases where total numbers are different from the *N* for that group, the clinical data was not available on the chart. A single digit in the length of follow-up indicates that their last documented follow-up was while in the house and the patient did not present for further outpatient follow-up at our institution

		Early	Late	*P* value
N		71	372	
Age				0.258
	Min	16	13	
	Max	83	92	
	Mean	49	52	
Gender				0.173
	M	41	182	
	F	30	190	
Tumor volume (cm^3)				*< 0.001*
	Min	0.16	0.008	
	Max	90.59	124.75	
	Mean	12.33	4.64	
Knosp score				*0.0006*
	0	9	85	
	1	13	87	
	2	19	60	
	3	6	36	
	4	14	22	
Diagnosis				0.692
	Initial	59	316	
	Recurrent	12	56	
Surgical approach				*< 0.001*
	Endoscopic	40	41	
	Microscopic	28	331	
	Transcranial	3	0	
Pathology				0.640
	Nonfunctioning	15	79	
	Prolactinoma	11	48	
	ACTH +	7	65	
	GH +	7	28	
	FSH/LH +	24	108	
	TSH +	0	0	
	Mixed	7	42	
Last follow-up (days)				0.856
	Min	2	2	
	Max	1819	2302	
	Mean	470.46	458.90	

Emphasis indicated significant *p*-values < 0.05

groups. Visual acuity was stable/improved in 93.30% of early MRI patients and 85.34% of late MRI patients ($p = 0.153$). Visual fields were stable/improved in 96.77% of early and 99.33% of late ($p = 0.136$). Extra-ocular movements (EOM) were stable/improved in 100% of patients in both groups (Fig. 3).

Multivariate analysis

Logistic analysis for return to OR showed that the presence of residual on postoperative scan ($p = 0.003$) and age ($p = 0.014$) were significant predictors of return to the OR. Volume by quartile approached significance ($p = 0.055$). For progression to radiosurgery, the presence of residual on postoperative scan ($p = 0.047$) was a significant factor. For worsened visual acuity, tumor recurrence ($p = 0.004$), volume ($p = 0.011$), and age ($p = 0.031$) were significant factors. There were no events of EOM worsening to perform a logistic model, and there were no significant variables predicting worsening of visual fields. For multivariate analysis, tumor size was divided into categorical values based on distribution percentiles. The 25th percentile was tumors < 1 cm^3, 25–75th percentiles were tumors 1–5 cm^3, and the 75th percentile was tumors > 5 cm^3. Multivariate analysis is summarized in Table 4.

Imaging costs

At our institution, MRI brain with and without contrast had an average facility fee of $2953.26. The associated physician professional fees were $274.20, for a total associated cost of $3227.46. CT brain without contrast had a facility fee of $1499.89, with professional fees of $102 for a total associated cost of $1601.89.

Discussion

In this study, our results indicated that patients undergoing early MRI have a statistically higher rate of return to the OR and that early MRI calls a significantly higher percentage of residual but no difference in long-term clinical outcomes. Of note, on the 3-month follow-up, 13.5% of these initial positive results were subsequently read as negative for residual. Also, there were significant differences in tumor size, invasiveness, and surgical approach between our two demographic groups.

Timing of MRI

The argument for early postoperative MRI after transsphenoidal resection has evolved with improving MRI techniques. Early studies found significant interference in identifying residual tumor in the setting of acute postoperative changes such as site packing, hemorrhage, undescended residual tumor and thus recommended delaying MRI until changes have resolved in 3–4 months [2–4, 6]. More recent studies have found that early postoperative MRI is accurate in identifying residual tumor and have recommended early MRI, including dynamic sequence within

Table 2 Clinical outcomes data for return to OR, time to return to OR, radiosurgery, identification of residual, and final visual acuity, visual fields, and extra-ocular movements testing. EOM = extra-ocular movements

		Early	Late	*p* value
Return to OR		12 (16.9%)	18 (4.8%)	*< 0.001*
Radiosurgery		0	9 (2.4%)	0.366
Time to radiosurgery (days)	Min	NA	90	
	Max	NA	1096	
	Mean	NA	427.67	
Residual identified on MRI (% per available study results)		37 (52.1%)	110 (29.6%)	*< 0.001*
Visual acuity at last exam		45	191	0.153
	Stable/improved	42 (93.3%)	163 (85.3%)	
	Worse	3 (6.67%)	28 (14.66%)	
Visual fields at last exam		62	302	0.136
	Stable/improved	60 (96.8%)	300 (99.3%)	
	Worse	2 (3.22%)	2 (0.66%)	
EOM at last exam		66	311	NA
	Stable/improved	66 (100%)	311 (100%)	
	Worse	0 (0%)	0 (0%)	

Emphasis indicated significant *p*-values < 0.05

72 h of surgery [12], diffusion-weighted imaging 1–7 days post-operatively [4], and high-resolution volumetric scans within the first 30 days after surgery [9].

One of the common rationales for early postoperative imaging is that it allows surgeons to intervene earlier for residual tumor [9, 12]. However, in our series, timing for return to the OR was not significantly different, likely reflecting the slow growth of pituitary adenomas. Our institutional practice pattern reflected a model of waiting for non-emergent re-intervention for extremely large tumors. This allows residual tumor to descend into the resection cavity and for postoperative blood products to resolve for better visualization during surgery.

Early identification of residual tumor may aid in developing a radiosurgery plan, which is another argument for early performance of MRI after pituitary surgery. However, radiosurgery plans are created in a delayed fashion. A multi-institutional study recommended obtaining planning imaging at 2–3 months to allow time for recovery from surgery and

Table 3 Patient details for return to OR in each imaging category

Return to OR reason	Number	Patient presentation	Surgery performed
Early MRI	*12*		
CSF leak	2	CSF rhinorrhea	Endoscopic exploration and repair
Sinus pathology	1	Chronic rhinosinusitis	Endoscopic exploration and repair
Neurological symptoms	2	Loss of vision	Re-exploration
		Seizures 2/2 mass effect from extra-sellar adenoma	Laser ablation of hippocampus
Endocrinological	1	Persistent Cushing disease	Re-resection
Recurrence	6	Residual	Re-resection
Late MRI	*18*		
CSF leak	2	CSF rhinorrhea	Endoscopic exploration and repair
Sinus pathology	3	Chronic rhinosinusitis	Endoscopic exploration and repair
Neurological symptoms	2	Acute vision loss	Re-exploration
		CN6 palsy	Oculoplastic
Negative pathology	1	Pathology showed no tumor	Re-resection
Recurrence/residual	10	Recurrence/residual	Re-resection

Emphasis indicated total number for each category which is subdivided into subtypes below

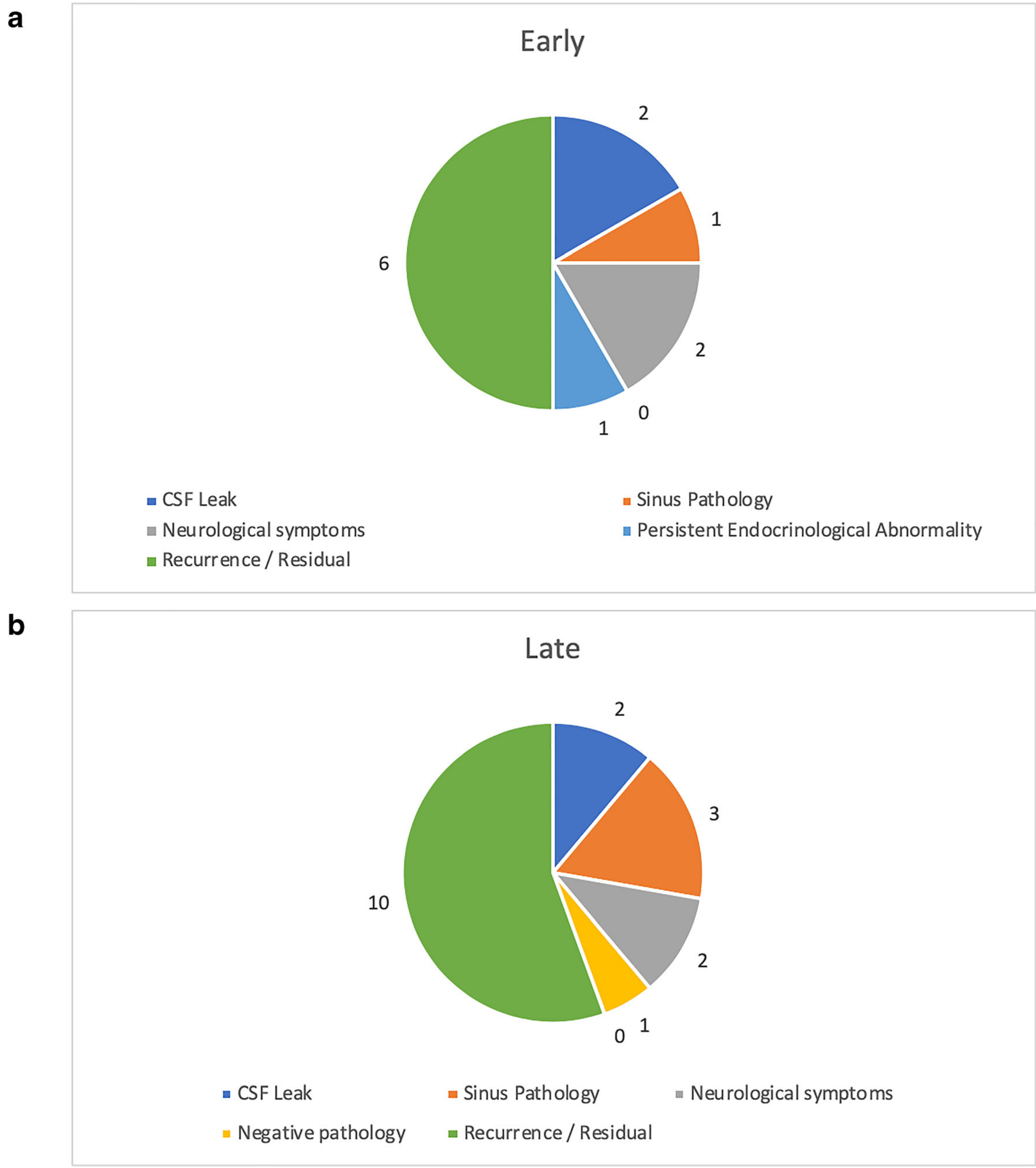

Fig. 2 Distribution of reasons for return to OR in early (**a**) vs late (**b**) MRI patients by the number of patients

postsurgical changes on MRI to subside [10]. Our study only found progression to radiosurgery in patients undergoing late MRI, indicating that earlier data did not help progress these patients to adjuvant treatment. In this setting, a 3-month MRI when postoperative changes have resolved, and descent of residual tumor has completed and gives more than enough time for planning and performance of radiosurgery as indicated.

Current practices

At our institution, patients receive an MRI at 3 months, 6 months, and 1 year after surgery then yearly thereafter. This is similar to many regimens reported in the literature. In 1993, Dina et al. reported typical follow-up times of 6–12 months postsurgery [2]. Yoon et al. reported a relatively large population of patients that underwent early postoperative MR imaging within 7 days after surgery and follow-up MR imaging every 6 months [12]. In their study, Wu et al. used high-field MRI follow-up for recurrence at 1, 3, and 6 months after operation and at 6-month intervals thereafter or when clinically indicated [11]. Kilic et al. sought to establish a standardized protocol for follow-up and performed MRI at 24 h, 3 months, 6 months, and 9 months, and at 1 year or more postsurgery [5]. Our results indicate that the timing of MRI does not change long-term patient outcomes,

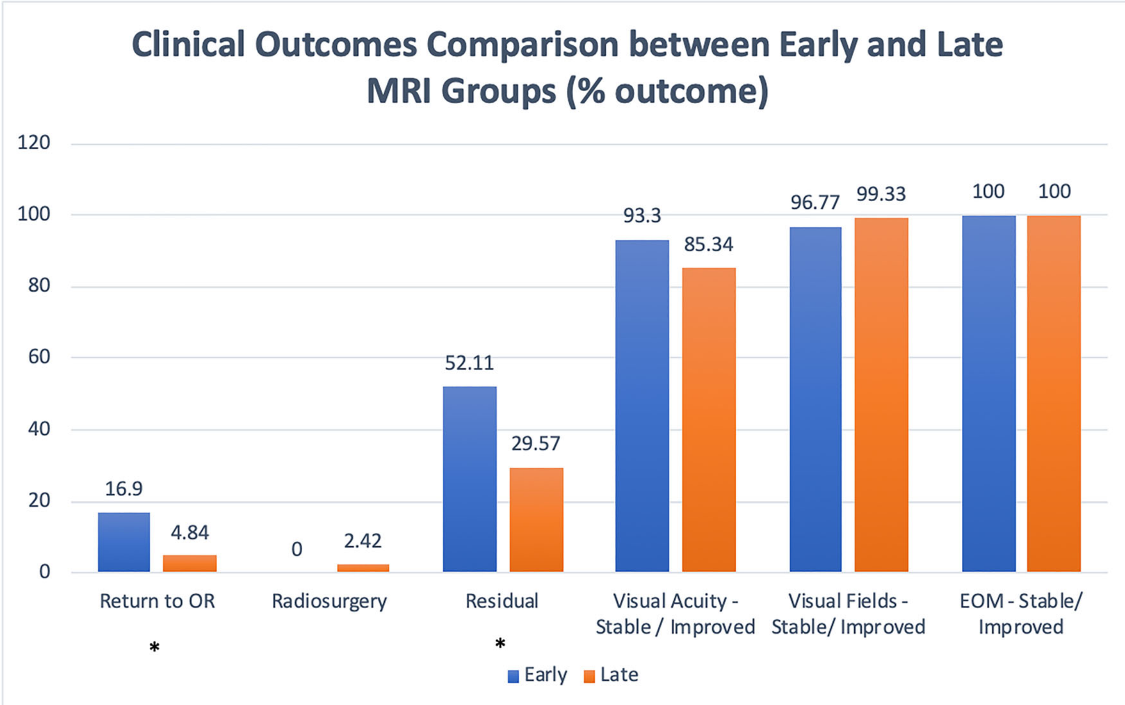

Fig. 3 Comparison of clinical outcomes between early and late MRI (asterisk = statistically significant)

and although early MRI is associated with higher rates of return to the OR, it may falsely identify residual.

Imaging costs

Limited studies have previously looked at costs associated with pituitary surgeries with estimate costs for the hospital stay ranging from $34,943.13 [1] to $76,228 [8]. Patel et al. directly addressed the issue of cost in their study and found utility to immediate postoperative volumetric MRI to evaluate resection bed, noting a low re-operation rate in the setting of asymptomatic patients. They recommended scanning if worsened or unchanged postoperative vision to determine the need for re-operation or if there is residual tumor that would need re-operation [9]. This indicates the importance of having an institutional protocol for the timing of imaging.

Table 4 Logistic models for outcomes of return to OR, radiosurgery, and postoperative worsening of visual acuity with odds ratios and *p* values

Variable	Odds ratio	*p* value
Return to OR		
Residual on postop scan	3.58 (1.56–8.21)	0.003
Age (per 10 years)	0.74 (0.58–0.94)	0.014
Volume		0.055
< 1 cm^3	Reference	
1–5 cm^3	0.93 (0.25–3.45)	0.087
> 5 cm^3	2.54 (0.75–8.64)	0.227
Missing	3.92 (1.02–15.01)	0.029
Radiosurgery		
Residual on postop scan	4.13 (1.02–16.75)	0.047
Visual acuity		
Recurrent	4.12 (1.57–10.77)	0.004
Volume		0.011
< 1 cm^3	Reference	
1–5 cm^3	3.94 (0.99–15.62)	0.086
> 5 cm^3	7.64 (1.77–33.07)	0.002
Missing	0.54 (0.05–5.70)	0.010
Age (per 10 years)	1.35 (1.03–1.77)	0.031
Residual on postop scan	0.52 (0.21–1.30)	0.162

The addition of an MRI scan adds several thousand dollars to an already expensive cost. MRI costs at our institution are estimated at $3227.46 for MRI with and without contrast for the year 2019. CT scan can be effective in identifying complications requiring early return to the operating room and could be used in the vast majority of cases as a further cost saving measure, at a cost of $1601.89 at our facility. Although patients may not directly see this cost, depending on the reimbursement model of the healthcare system, they are reflected on either the patient or the hospital as an unnecessary financial burden. This reflects the ethos of movements such as the Choosing Wisely campaign to limit unnecessary medical tests [4].

Limitations

We did find statistical differences in volume between the two groups. The group undergoing early MRI had a larger average tumor volume. Although this may be simply due to heterogeneity of data, it does fit the fact that larger tumors would have higher rates of re-imaging because of the extent of surgery or that the operating surgeon would have a lower threshold to re-image earlier when planning for a repeat surgery.

This is a retrospective review with small cohorts of secondary treatments. Additionally, our institution is a tertiary referral center and patients often receive follow-up care and monitoring at remote institutions which can limit clinical and radiographic follow-up data available in our system for both clinical outcomes and secondary treatments. Prospective studies with standardized imaging criteria and follow-up could further address the question of the ideal postoperative imaging protocol.

Conclusion

After surgical treatment of pituitary adenoma, MRI obtained before 3 months is associated with higher rates of return to OR but no difference in long-term clinical outcomes. Due to cost efficiency, we argue for a delayed first postoperative MRI. The timing of MRI should also be governed by other factors such as large pituitary macroadenomas or postoperative complications. We recommend a consistent institutional protocol for determining the most cost-effective follow-up of postoperative pituitary patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name of institute/committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval was waived by the local Ethics Committee of the Colorado Multiple Institutional Review Board (Protocol 17-2116) in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Informed consent For this type of study, (retrospective) formal consent is not required.

General disclosures A Samy Youssef, MD PhD: Mizuho America: royalties

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