Title: The Optimal Time for Post-Operative Magnetic Resonance Imaging of the Sella in Patients with Pituitary Adenoma

Running Title: Post-Operative Magnetic Resonance Imaging of the Sella

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Abstract

Introduction : Magnetic resonance imaging (MRI) is the preferred neuroradiologic tool for evaluating the sellar region. Pituitary adenomas account for about 15% of primary intracranial tumors. The optimal time for post-operative MRI of CNS neoplasms is 48 hours after surgery. Nevertheless, controversy exists regarding the timing of post-operative MRI in the sellar region. This study analyzed the sellar MRI findings of patients with pituitary adenoma at different times before and after surgery. Finally, we suggest the optimal time for post-operative sellar MRI imaging in patients with pituitary adenoma.

Materials and Methods: A total of 28 patients with pituitary adenoma were evaluated. All patients did four sellar MRIs; the first MRI was done before surgery, and three remainings were done as follows: 48 hours, two weeks, and three months after the surgery. Finally, the MRI findings at different times were compared to each other.

Results: We resulted that the pituitary gland and adenoma signals were constant in all sequences over time. The signal of the packing material showed no differences in T1-weighted and T1-weighted with contrast sequences but showed changes in T2-weighted sequences.

Discussion: In contrast to other intracranial neoplasms, in patients with pituitary adenoma, there were no apparent changes in MRI signal intensity during the 3-month after surgery. There was also no superiority of one time over another for performing follow-up imaging.

Keywords. Post-operative Imaging, Sellar region, Pituitary adenoma

Introduction

Pituitary adenomas account for about 15% of primary intracranial tumors [1-3]. Except for prolactinoma, the treatment of choice in pituitary adenoma is surgical excision [4 5]. Post-operative imaging has an important role in detecting possible surgical complications, tumor residue, and treatment planning [6 7]. MRI is the preferred neuroradiologic method of evaluating the sellar region [8 9]. The reason for the widespread acceptance of the MRI is the appropriate contrast among the different elements of the soft tissue [10]. Generally, the optimal time for early post-operative MRI in CNS lesions is 48 hours post-surgery [11-13]. Nevertheless, no guidelines determine the best time for post-operative imaging in patients with pituitary adenomas [14].

We analyzed the pituitary gland, adenoma, and packing material signals during three months after surgery in all sequences and finally proposed the optimal time for post-operative imaging after pituitary adenoma surgery.

Materials and Methods

Patient Population

A total of 28 patients with pituitary adenoma who refer to the Department of Neurosurgery at Firoozgar University Hospital in Tehran, Iran, from July 2019 to March 2021 were examined. The study was conducted with the approval of the Ethics Committee of the Iran University of Medical Sciences. It was in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments.

The inclusion criteria were:

- A diagnosis of pituitary adenoma.
- Being a candidate for endoscopic transsphenoidal surgery.
- No history of previous surgery or other therapies such as irradiation and dopamine agonist therapy.

All patients had pre-operative contrast-enhanced MRI of the sellar region to determine the extent of the tumor and involvement of adjacent structures. Pre-operative, endocrinologic, and ophthalmologic evaluations were carried out for all patients.

Surgical technique

All patients underwent an endoscopic endonasal approach under general anesthesia. The endoscopic equipment used included a 0° and 30°, 4 mm rigid endoscope (Karl Storz; Germany), a full high definition (HD) camera (Image 1, H3-Z), and a wide view HD screen. Generally, the approach was through the right nostril, but the left side was used if there was a significant septal deviation to the right. The sellar floor was reconstructed using a fat pad

covered by Surgicel and gelfoam. Histopathologic analysis was performed to establish the diagnosis.

Post-operative MRI

The MRI was performed with a 1.5 T system (Siemens Medical Solutions). The imaging protocol included non-enhanced T1- and T2-weighted and post-contrast T1 images with a 5-mm section thickness of the axial, coronal and sagittal planes. All patients had a sellar MRI before surgery and three sellar MRIs at 48 hours, two weeks, and three months after surgery.

Imaging analysis

All MR images were interpreted concerning the contents of the sella. The contents of the sella were divided into three compartments: the pituitary gland, pituitary adenoma, and adipose tissue used to pack the sella. The signal for each compartment was recorded in the T1-weighted, T2-weighted, and T1-weighted with contrast sequences at different times.

Statistical Analysis

Statistical analysis, including descriptive data analysis, was performed using SPSS Statistics (ver. 23.0; IBM; USA). The sellar contents signals at the different times were considered non-parametric and were evaluated using the Friedman and sign tests. Two-sided p-values of less than 0.05 were considered statistically significant.

Results

Demographic and clinical aspects

The mean age of the participants was 45.8 years. 60.7% were female, and 39.3% were male. The most common complaint at presentation was the enlargement of the extremities, which affected eight patients (28.6%). A visual disturbance occurred in 7 patients (25%), while six patients (21.4%) had a headache. Ten patients (35.7%) had nonfunctional pituitary adenoma, 10 (35.7%) were diagnosed with acromegaly, 6 (21.4%) had prolactinoma, and 2 (7.1%) had an ACTH-producing tumor.

Of the 28 patients, 25 had macroadenomas, and three had microadenomas. After surgery, a residual tumor (incomplete removal) was confirmed in 4 patients (14.2%). Post-operative Cerebrospinal fluid (CSF) rhinorrhea occurred in only 8 cases that improved after conservative treatment. Seven (25%) patients developed transient post-operative diabetes insipidus (DI) during hospitalization. On ophthalmological examination, 16 (57.1%) patients showed visual field deficits. The demographic and clinical characteristics are shown in Table 1.

MRI of the pituitary gland

In 27 of 28 patients (96.4%), the pituitary gland in the T1-weighted sequence was isointense, and one (3.6%) was hyper-intense. In the T2-weighted sequence, 27 (96.4%) patients were

isointense, and one (3.6%) was hyperintense. In the T1-weighted with contrast sequence, the pituitary glands of all patients were hyperintense. The post-operative MR images had similar results at 48 hours, two weeks, and three months after surgery. An overview of the pituitary gland signal is shown in Table 2 (Figure 1-3).

MRI of pituitary adenoma

T1-weighted pituitary adenoma signals were hypointense in 14.3% of patients, isointense in 21.4%, hyperintense in 53.6%, and mixed in 10.7%. The T2-weighted sequence was hypointense in 17.9%, isointense in 46.4, hyperintense in 32.1%, and mixed in 3.6%. The T1-weighted sequence with contrast was hyperintense in 92.9% of patients and mixed in 7.1%. In post-operative imaging, only four patients showed tumor residue; the signal intensity showed no difference at various times (Table 5). An overview of the MRI characteristics of the pituitary adenomas is given in Table 3 (Figure 1-3).

MRI of Packing Material

The sellar floor was reconstructed with an autografted adipose tissue covered by surgicel and gelfoam. In the first post-operative MRI of the T1-weighted sequence, the signal of these materials in 7.1% of patients was hypointense, 46.4% was hyperintense, and 46.4% was mixed-intense. The second MRI showed hypointense in 14.3%, hyperintense in 39.3%, and mixed intensity in 46.4%. The third MRI showed hypointense in 10.7%, hyperintense in 46.4%, and mixed intensity in 35.7%. The signal intensities of T1- and T2-weighted images and post-contrast images are indexed in Table 4

Discussion

MRI is currently the preferred neuroradiologic tool for evaluating the sellar region. Post-operative MRI is routinely performed to determine residual or recurrent tumors as well as possible complications [6 7]. Although the optimal time for post-operative MRI for a CNS neoplasm is 48 hours after surgery, there is controversy about the timing for the pituitary adenoma [11-14]. Several studies recommend that the follow-up MRI should not be done immediately after transsphenoidal surgery because of post-operative changes such as swelling, blood products, and packing materials inserted into the sella can lead to misinterpretation of the MRI.These studies recommend waiting for their regression [15 16].

Steiner et al. evaluated pre-operative and post-operative MR images of 25 patients diagnosed with pituitary adenomas. They recommended that a follow-up MRI should be done 4-6 months after surgery [17]. On the other hand, some studies have reported that the best time for post-operative MRI was a few days after surgery. Kilic et al. assessed 80 patients with

pituitary adenomas and found that the best follow-up imaging was 24 hours after transsphenoidal surgery. During this period, inflammation is in the early phase, and the packing material has not degraded and can easily be identified on the MR image. Additionally, blood degradation products, such as methemoglobin, have not yet formed and can easily be differentiated from a residual tumor [14]. The current study found no time preference for the performance of post-operative MRI.

We found that the pituitary gland signals in most patients were isointense in the T1- and T2-weighted and hyperintense in the T1-weighted with contrast. The pituitary gland showed constant signals over the three months post-surgery and was well demarcated from the surrounding tissue. Most previous articles reported only good delineation of the pituitary gland after surgery and did not define the signal intensity in each sequence.

Kilic et al. concluded that the early post-operative MRI and delayed MRI delineated the pituitary gland [14]. Yoon et al. did not explain the delineation and signal intensity of the pituitary gland and only reported changes in its configuration after surgery [18]. Kramer et al. found that the normal gland was not visible in most patients in early post-operative MRI [19]. Steiner et al. reported that, in 22 of 25 patients, the pituitary gland was well-delineated after surgery but did not compare this result with later follow-up imaging [17]. Dina et al. reported that in the early post-operative period, the pituitary gland was remarkably similar to its pre-operative appearance [20]. Rodriguez et al. evaluated the size and shape of the pituitary gland after surgery and compared imaging according to these criteria [16].

Although only six patients were found to have a residual tumor, the tumor and packing material were well delineated in all of them. In all patients, the signal for the adenoma in all sequences was constant over time. Despite using the same materials for packing, their signals were different, probably because of the presence of blood that had stained the gelfoam and Surgicel. packing material MRI signals were compared, and it was concluded that there were meaningful differences in their intensity only in the T2-weighted sequence (Table 5). We observed that the T2 signal intensity of the packing material changed from hyperintense to hypointense. This shift probably was caused by a decrease in the water content and concentration of macromolecules, which have short T2 relaxation times [21].

Kilic et al. could not differentiate a residual tumor in one-third of patients in the early post-operative MRI because of blood in the tumor bed [14]. Stiner et al. reported that the adenoma's signal and its remnant were constant in all patients except one. They performed post-operative MRI once, compared it with pre-operative MRI, and could not differentiate residual tumor from implanted material [17]. In contrast to other studies that assessed the shape

of the sellar element, the current study compared post-surgical MRI statistically based on the signal intensity of the sellar contents. The change in signal intensity of the sellar elements is a more objective criterion than their shape.

We concluded that in patients with pituitary adenoma, in contrast with other intracranial neoplasms, there were no apparent changes in MRI signal intensity over the three-month post-surgical period. So there is no advantage to the time of follow-up imaging in patients with pituitary adenoma. Consequently, unlike previous documentation, the Imaging time of the patient with pituitary adenoma was unimportant, and MRI could be performed any time after surgery.

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Table 1. Demographic and clinical characteristics

Case No	Age (yrs.), Sex	presentation	Size of tumor	Type of adenoma	CSF leak*	Residue
1	40,F	Headache	macroadenoma	prolactinoma	+	+
2	43,F	enlargement of extremities	macroadenoma	GH-secreting		
3	52,M	Obesity	microadenoma	ACTH-secreting		
4	42,F	Headache	macroadenoma	GH-secreting		
5	38,M	Infertility	macroadenoma	nonfunctional	+	
6	47,F	enlargement of extremities	macroadenoma	GH-secreting		
7	49,F	Visual disturbance	macroadenoma	nonfunctional		
8	50,F	Infertility	macroadenoma	prolactinoma	+	
9	54,M	enlargement of extremities	macroadenoma	GH-secreting	+	
10	51,M	Infertility	macroadenoma	prolactinoma		
11	55,F	Visual disturbance	macroadenoma	nonfunctional		+
12	38,F	Headache	macroadenoma	nonfunctional		
13	47,F	Visual disturbance	macroadenoma	nonfunctional	+	
14	44,F	enlargement of extremities	macroadenoma	GH-secreting		
15	49,F	enlargement of extremities	macroadenoma	GH-secreting		
16	48,M	Infertility	macroadenoma	nonfunctional		
17	50,F	Visual disturbance	macroadenoma	prolactinoma		
18	33,F	enlargement of extremities	macroadenoma	GH-secreting		
19	62M	Headache	macroadenoma	nonfunctional		
20	44,M	enlargement of extremities	macroadenoma	GH-secreting		
21	51F	Headache	macroadenoma	GH-secreting	+	+
22	43,M	Obesity	microadenoma	ACTH-secreting		
23	39,F	Headache	macroadenoma	nonfunctional	+	
24	55,M	Headache	macroadenoma	prolactinoma		
25	39,M	enlargement of extremities	microadenoma	GH-secreting		
26	42,F	Visual disturbance	macroadenoma	nonfunctional	+	
27	40,F	Visual disturbance	macroadenoma	prolactinoma		+
28	40,M	Infertility	macroadenoma	nonfunctiona		

* CSF denote Cerebrospinal fluid

Table 2. MRI characteristics of the Pituitary gland signals in three different sequences at time intervals

Sequence	T1				T2				T1 with contrast			
Signal Evaluation Time	PO*	48h**	2nd week	3th month	PO	48h	2nd week	3th month	PO	48h	2nd week	3th month
Hypo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Iso	96.40	96.40	96.40	96.40	96.40	96.40	96.40	96.40	0.00	0.00	0.00	0.00
Hyper	3.60	3.60	3.60	3.60	3.60	3.60	3.60	3.60	100	100	100	100
Mixed	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

* PO=Preoperative; ** h=Hour.

Table 3. MRI characteristics of the pituitary adenoma signals in three sequences at time intervals

Sequence	T1				T2				T1 with contrast			
Signal Evaluation Time	PO*	48h**	2nd week	3th month	PO	48h	2nd week	3th month	PO	48h	2nd week	3th month
Hypo	14.3	0	0	0	17.9	25	25	25	0.0	0	0	0
Iso	21.4	25	25	25	46.4	50	50	50	0.0	0	0	0
Hyper	53.6	75	75	75	32.1	25	25	25	92.9	100	100	100
Mixed	10.7	0	0	0	3.6	0	0	0	7.1	0	0	0

* PO=Preoperative; ** h=Hour.

Table 4. MRI characteristics of the packing material in three sequences at time intervals

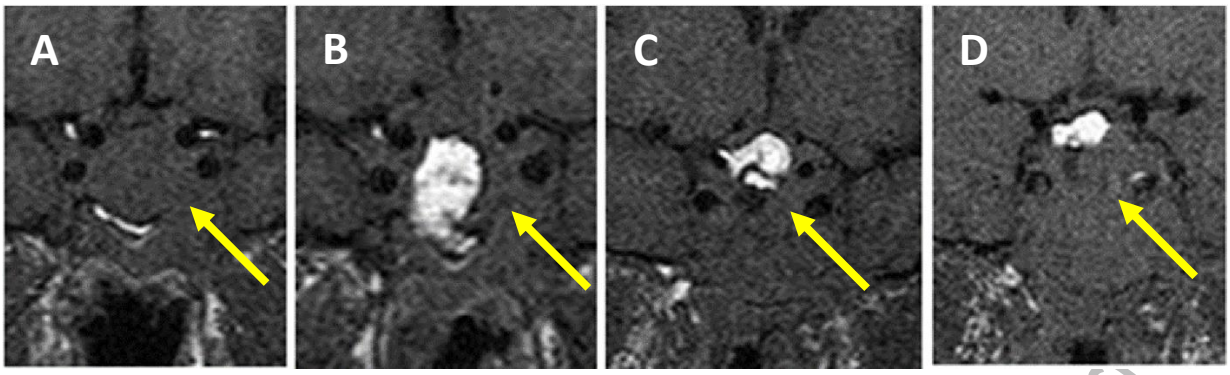
Sequence	T1			T2			T1 with contrast		
Signal Evaluation Time	48h*	2nd week	3th month	48h	2nd week	3th month	48h	2nd week	3th month
Hypo	7.1	14.3	10.7	3.4	3.6	35.7	7.1	14.3	10.7
Iso	46.4	39.3	46.4	10.7	7.1	10.7	46.4	39.3	46.4
Hyper	46.4	46.4	35.7	35.7	35.7	17.9	46.4	46.4	35.7
Mixed	100	100	92.9	50	53.6	28.6	100	100	92.9

* h=Hour.

Table 5. Signal differences between time intervals in the patient who underwent pituitary adenoma surgery

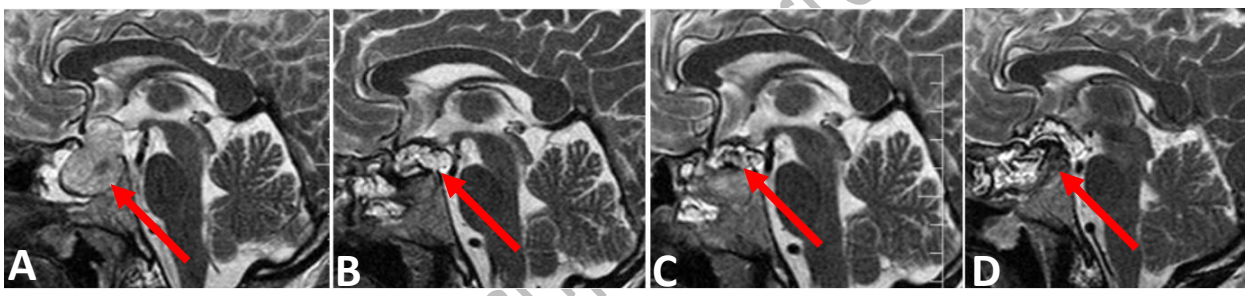
	Groups	Sellar Component					
		Pituitary Adenoma			Packing Material		
		T1	T2	T1 with contrast	T1	T2	T1 with contrast
(P-value)	PO* & 48h**	P<0.001	P<0.001	P<0.001	-	-	-
	PO* & 2nd week	P<0.001	P<0.001	P<0.001	-	-	-
	PO* & 3th month	P<0.001	P<0.001	P<0.001	-	-	-
	48h** & 2nd week	-	-	-	0.625	1.000	0.500
	48h** & 3th month	-	-	-	0.375	0.001	1.000
	2nd week & 3th month	-	-	-	0.250	P<0.001	0.687

* PO=Preoperative; ** h=Hour.



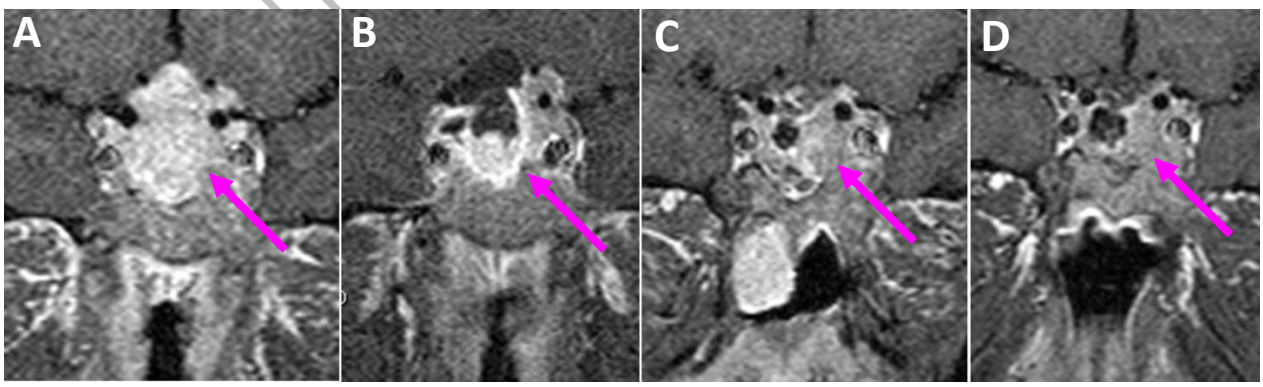
Figure, 1. *T1 weighted magnetic resonance Imaging of sella*

Tl -weighted magnetic resonance Imaging from sellar region preoperatively (A) and postoperatively in 48 hours (B), 2 weeks (C), 3 month (D) after surgery. The arrays show sellar region



Figure, 2. *T2 weighted magnetic resonance Imaging of sella*

Sagital T2-weighted MRI from sellar region preoperatively (A) and postoperatively in 48 hours (B), 2 weeks (C), 3 month (D) after surgery. The arrays show sellar region



Figure, 3. *T1 weighted with contrast magnetic resonance Imaging of sella*

Coronal contrast enhanced Tl -weighted MRI from sellar region preoperatively (A) and postoperatively in 48 hours (B), 2 weeks (C), 3 month (D) after surgery. The arrays show sellar region