Original Article

# Multiparametric MRI Findings association with Pathological Features and hormonal secretion in Patients with Pituitary Macroadenoma: A Comprehensive Study

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## Abstract

**Background:** Pituitary macroadenoma is a global health concern. Advanced imaging techniques, such as multiparametric magnetic resonance imaging (MRI), have emerged as valuable tools for comprehensively evaluating macroadenomas. This study aimed to evaluate the association between multiparametric MRI findings, pathological features, and type of secretion in patients with pituitary macroadenoma.

**Materials and Methods:** This cross-sectional study evaluated the association between multiparametric MRI findings and pathological features in patients with pituitary macroadenoma. Patients with pituitary macroadenoma referred to Loghman Hakim Hospital (Tehran-Iran) in 2023 were assessed. Preoperative MRI, including T1W, T2W, DWI, ADC, and CE-MRI, were evaluated for signal intensity, maximum diameter, and tumoral extension. The association between the results of MR imaging and the pathologic findings of the resected macroadenoma was assessed.

**Results:** Forty-five patients were assessed. The mean age was 48.22 ± 14.58 years, and 55.6% of the patients were male. Most patients (48.9%) had isointense lesion in T1W, and most lesions (57.8%) had heterogeneous signals in T2W. Apparent diffusion coefficient levels (ADC) had no diagnostic value for predicting pathologic subtypes. The most invasion was to the infrasellar among macro adenomas (P-value: 0.037). Among patients with gonadotroph pathology results, invasion to the third ventricle with heterogeneous signal on T2 was more common (P-values<0.05). The mean tumor volume is higher in the Prolactin (PRL) secreting type compared to other categories (P-value: 0.002).

**Conclusion:** Multiparametric MRI helps predict the pathological diagnosis of pituitary macroadenoma.

**Keywords:** Adenoma, Pituitary tumor, Multiparametric magnetic resonance imaging, Pathology, Hormone secretion, Macroadenoma, ADC

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## Introduction

Pituitary adenomas (PA) are primary neoplasms that arise in the pituitary gland. PAs are classified based on their size. Those smaller than 10 mm are known as microadenomas, and the rest as macroadenomas[1]. PAs are classified as functional or non-functional based on

their hormone-secreting capabilities. Functional PA manifests itself with endocrine-related clinical phenotypes. These phenotypes are associated with different symptoms of hyperpituitarism or hypopituitarism, depending on the level of hormone secretion under the influence of PA. Patients with non-functional PA do not secrete any detectable hormones but are clinically symptomatic and may present with mass effects such as decreased vision and headache. About one-third of PAs are pituitary "incidentalomas" that are asymptomatic. Incidentalomas are often detected incidentally during unrelated imaging or postmortem examinations[2,3].

PA is the third most common central nervous sysytem (CNS) tumor among adults, accounting for 15% of all CNS tumors, the vast majority of which are benign PA[4]. The global prevalence is estimated to be between 68 and 115 per 100,000. Because of their slow growth rate, PAs tend to present insidiously with nonspecific symptoms, so accurate prevalence estimates remain challenging. A meta-analysis based on autopsy and radiological studies estimated that PA occurs in about 16.7% of the population. A significant part of these cases is believed to be diagnosed randomly without clinical symptoms[5-8].

Classification of PA based on size (microadenoma vs. macroadenoma) is frequently used today, but this classification alone may not accurately predict symptoms or the need for treatment. Larger PAs often have pressure effects and symptoms, but there is no precise size that consistently causes symptoms. Clinical decision-making should be based on signs and symptoms, not size alone. Hormone production and immunohistochemical staining can be used to classify PA based on the predominant hormone and pituitary-specific biomarkers expressed by the tumor. Based on the expression of pituitary hormones and pituitary-specific transcription factors, PA is classified into eight subtypes: silent gonadotroph, corticotroph, somatotroph, thyrotrophin, lactotroph, neurohormonal Pit-1, null cell, and double/triple non-functional pituitary adenoma (NFPA). However, further studies are needed to establish a strong correlation between histopathological factors and the clinical behavior of PAs[9].

At present, an important part of diagnosing and evaluating PAs mainly depends on magnetic resonance imaging (MRI). Several studies have shown that MR signals can predict some histological features of PA, but studies are still limited[10-12]. Therefore, this study aimed to investigate the relationship between multiparametric MRI findings with pathological features and the type of secreting hormone in patients with pituitary macroadenoma.

## Methods

This cross-sectional study was conducted on patients with pituitary macroadenoma referred to and operated at Loghman Hakim Hospital (Tehran-Iran) in 2023.

The inclusion criteria were confirmed diagnosis of pituitary macroadenoma based on clinical, radiological, and pathological findings, as well as preoperative MRI. The exclusion criteria were lack of MRI data, including low-quality or incomplete preoperative MRI that prevents accurate analysis; lack of pathologic specimens like lack of sufficient tumor specimens or many artifacts for adequate pathological analysis; receiving treatment for a pituitary macroadenoma such as surgery, radiation therapy, or drug therapy; having underlying disorders including Rathke's cleft cyst, craniopharyngioma, meningioma, pituitary hyperplasia, lymphocytic hypophysitis, metastatic tumors, sarcoidosis; pregnancy or breastfeeding, not having consent to participate to the study, having MRI contraindications such as implanted metal devices or severe claustrophobia.

Preoperative MRI scans of patients, including T1-weighted (T1W), T2-weighted (T2W), diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC), and contrast enhanced-MRI (CE-MRI) sequences, were retrieved. It was ensured that standard imaging protocols and techniques were used in all patients. Two expert radiologists assessed all MRI findings, and if there was a conflict between them, another expert radiologist assessed the imaging. ADC mass number was calculated with an oval region of interest (ROI) placed at the center of macroadenoma, with special care taken to ensure that adjacent structures were not covered by ROI. Moreover, the pons ADC number was obtained by putting an ROI in the central part of the pons Figure 1.

Tumor pathological samples were collected using surgical resection or biopsy methods. Standardized

histopathology techniques were used to process and stain the samples. The pathologic specimens were re-evaluated by an expert pathologist. Tumor composition, vascularity, presence of specific hormone-producing cells, and other relevant pathological features were evaluated. Clinical data were also collected from medical records, including

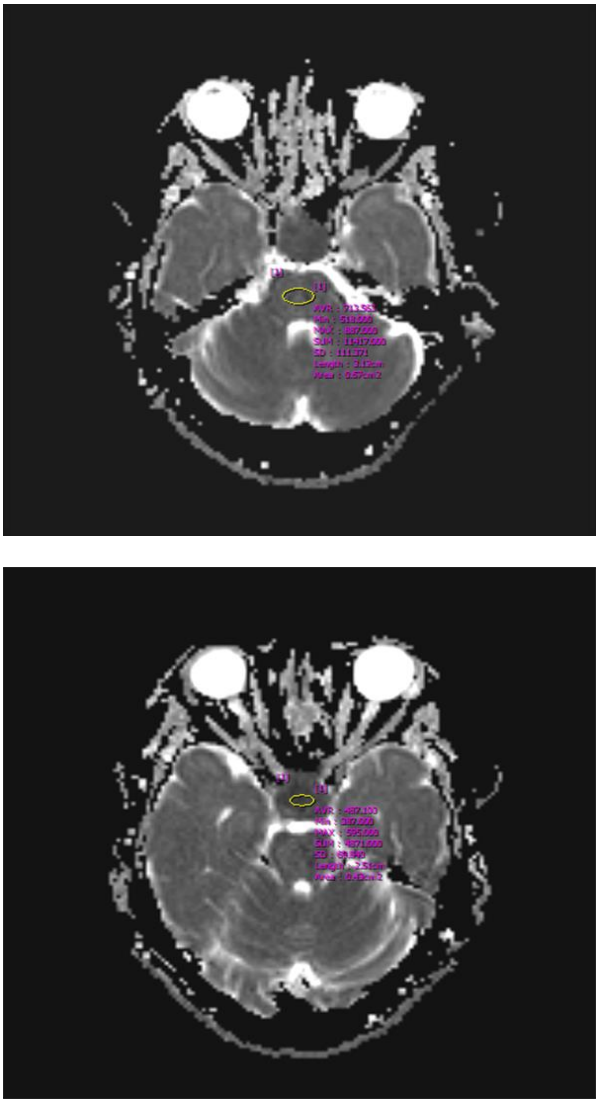


**Figure 1.** Axial ADC depicts the method of measurement of tumoral and pontine ADC using ROI.

demographic data, hormonal status, and clinical characteristics.

**Statistical analysis:** Mean, standard deviation, frequency, and percentage were used to describe the data. ANOVA test was used to compare numerical variables between groups, and chi-square and Fisher's exact test was used to compare between groups. Analyzes were performed using SPSS 25.0 statistical software. A P-value less than 0.05 was considered statistically significant.

**Ethics Statement:** Informed consent was obtained from all the patients involved in the study to participate in the study and to publish results. All patient information remained confidential. All stages of this study followed the Helsinki ethical principles. This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1402.425).

## Results

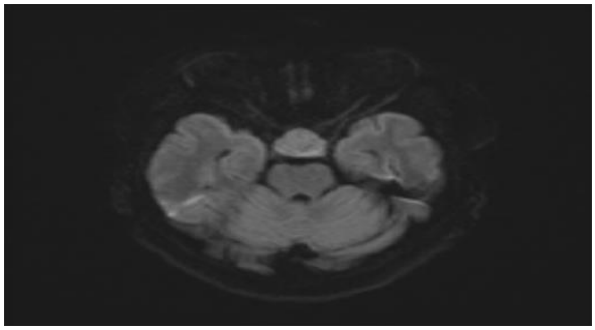
Forty-five patients were evaluated; 25 (55.6%) were male, and 20 (44.4%) were female. The mean age of all patients was 48.22 ± 14.58 years. Data on MRI findings are seen in Table 1. Figure 2 is one example of MRI in our patients.

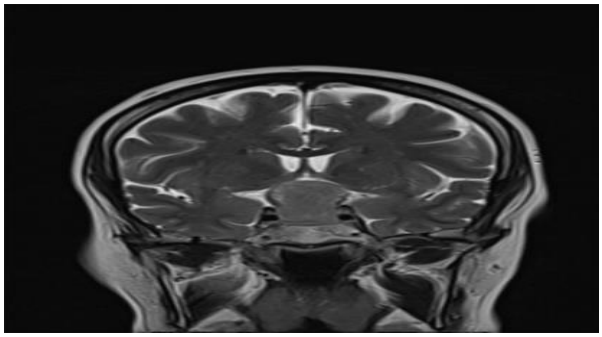
**Table 1.** MRI findings before surgery.

| | | N | % |
|---|---|---|---|
| **T1 signal** | Low | 10 | 22.2 |
| | ISO | 22 | 48.9 |
| | High | 2 | 4.4 |
| | Heterogeneous | 11 | 24.4 |
| **T2 signal** | Low | 1 | 2.2 |
| | ISO | 10 | 22.2 |
| | High | 8 | 17.8 |
| | Heterogeneous | 26 | 57.8 |
| **DWI** | Restricted | 27 | 60.0 |
| | W/O restriction | 18 | 40.0 |
| **Enhancement** | Homogeneous | 13 | 28.9 |
| | Heterogeneous | 27 | 60.0 |
| | Peripheral | 5 | 11.1 |
| | | Mean ± SD | |
| **Tumor ADC** | | 820.4 ± 554.73 | |
| **Pons ADC** | | 716.2 ± 187.7 | |
| **Consistency in MRI** | Solid | 19 | 45.2 |
| | Predominantly Solid | 17 | 40.5 |
| | Predominantly Cystic | 6 | 14.3 |
| **Infra. Sellar. Extension** | No | 15 | 34.1 |
| | Yes | 29 | 65.9 |
| **Extension to 3rd Ventricle** | No | 21 | 47.7 |
| | Yes | 23 | 52.3 |
| **Parasellar Extension** | No | 20 | 45.5 |
| | Yes | 24 | 54.5 |

Pathologic features of macroadenomas are seen in

Table 2. The most common type of secretion in macroadenomas is gonadotropins in our study (44.4%).





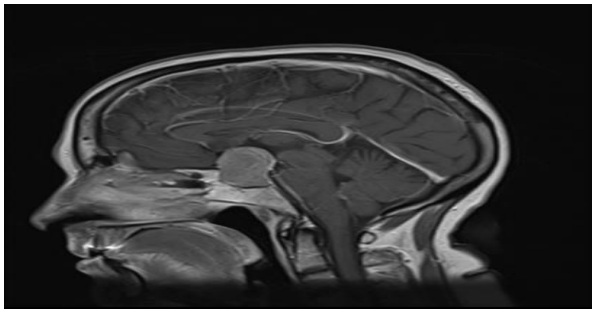


**Table 2.** Pathologic features of tumors after surgery.

| | | N | % |
|---|---|---|---|
| **Pathology** | PRL | 4 | 8.9 |
| | GH | 7 | 15.6 |
| | PR+GH | 5 | 11.1 |
| | FSH/LH | 20 | 44.4 |
| | Null cell | 6 | 13.3 |
| | Invasive | 3 | 6.7 |
| **PRL** | Densely granulated | 2 | 100 |
| | Sparsely granulated | 0 | 0 |
| | Acidophil stem cell | 0 | 0 |
| **GH** | Densely granulated | 3 | 50 |
| | Sparsely granulated | 3 | 50 |
| **GH+PRL** | Densely granulated | 0 | 0 |
| | Sparsely granulated | 1 | 100 |
| | Acidophil stem cell | 0 | 0 |

Table 3 assessed the relationship between MRI findings and pathological features in pituitary macroadenoma specimens, including tumor size. The mean of the three dimensions of the tumor (length, width, height) as a whole and separately was calculated based on different categories of T1W, T2W, and DWI. The mean tumor length was 11.7±27.44mm, the mean width was 12.19±24.67mm, and the mean height was 12.59±27.11mm. The larger tumors display heterogeneous signals in T1W and T2W sequences. There is no significant difference between small and large tumors in DWI restriction.

**Table 3.** Relationship between signal on T1W, T2W, and DWI with tumor dimensions (* Heterogeneous).

| | | Length | Width | Height |
|---|---|---|---|---|
| **T1 signal** | Total | 27.44±11.7 | 24.67±12.19 | 27.11±12.59 |
| | Low | 26.3±10.9 | 23.4±11.05 | 27.7±16.19 |
| | ISO | 26.23±10.93 | 23.41±8.71 | 24±9.31 |
| | High | 25±4.24 | 15.5±3.54 | 17±0 |
| | Hg*. | 31.36±14.83 | 30±18.17 | 34.64±13.24 |
| **T2 signal** | Low | 22± . | 13 ± . | 17 ± . |
| | ISO | 21.4±7.59 | 21.2±8.52 | 22.8±10.21 |
| | High | 25.25±6.34 | 25.13±11.44 | 23.25±8.63 |
| | Hg*. | 30.65±13.45 | 26.31±13.62 | 30.35±13.91 |
| **DWI** | Restricted | 27.93±9.46 | 25.11±10.8 | 29.26±11.4 |
| | W/O restriction | 26.72±14.71 | 24±14.33 | 23.89±13.9 |

The relationship between MRI findings and hormonal secretion of pituitary macroadenoma was evaluated in Table 4. Extension to the 3rd ventricle and heterogenous signal on T2 is significantly more common in gonadotroph adenomas.

Table 5 investigated the relationship between macroadenoma secreting hormone with tumor ADC and tumor sizes. The largest tumors were seen in the PRL group.

We evaluated tumor ADC to Pons ADC index between different hormonal categories of macroadenomas, and there was no statistically significant difference between them (P-value=0.26).

Relationship between demographic data and imaging or pathologic findings were evaluated. A significant difference was seen between the age of null cells and PRL groups. The average age of patients in the null cell group was approximately 26.67 years older than the PRL group (P-value=0.04).

**Table 4.** The relationship between MRI findings and hormonal secretion of pituitary macroadenoma.

| | | Pathology n(%) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **PRL** | **GH** | **PRL+GH** | **FSH/LH** | **Nullcell** | **Invasive** | **P-value** |
| **Consistency in MRI** | Solid | 0 (0.0%) | 4 (57.1%) | 5 (100.0%) | 5 (29.4%) | 3 (50.0%) | 2 (66.7%) | 0.1 |
| | Predominantly Solid | 3 (75.0%) | 3 (42.9%) | 0 (0.0%) | 9 (52.9%) | 1 (16.7%) | 1 (33.3%) | |
| | Predominantly Cystic | 1 (25.0%) | 0 (0.0%) | 0 (0.0%) | 3 (17.6%) | 2 (33.3%) | 0 (0.0%) | |
| | Cystic | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| **Infra/Sellar/Extension** | No | 1 (33.3%) | 3 (42.9%) | 2 (40.0%) | 7 (35.0%) | 2 (33.3%) | 0 (0.0%) | 0.8 |
| | Yes | 2 (66.7%) | 4 (57.1%) | 3 (60.0%) | 13 (65.0%) | 4 (66.7%) | 3 (100.0%) | |
| **Extension to 3rd Ventricle** | No | 2 (66.7%) | 6 (85.7%) | 4 (80.0%) | 6 (30.0%) | 3 (50.0%) | 0 (0.0%) | **0.03** |
| | Yes | 1 (33.3%) | 1 (14.3%) | 1 (20.0%) | 14 (70.0%) | 3 (50.0%) | 3 (100.0%) | |
| **Parasellar/Extension** | No | 2 (66.7%) | 5 (71.4%) | 3 (60.0%) | 7 (35.0%) | 2 (33.3%) | 1 (33.3%) | 0.5 |
| | Yes | 1 (33.3%) | 2 (28.6%) | 2 (40.0%) | 13 (65.0%) | 4 (66.7%) | 2 (66.7%) | |
| **T1 signal** | Low | 1 (25.0%) | 2 (28.6%) | 0 (0.0%) | 5 (25.0%) | 1 (16.7%) | 1 (33.3%) | 0.2 |
| | ISO | 1 (25.0%) | 4 (57.1%) | 5 (100.0%) | 7 (35.0%) | 3 (50.0%) | 2 (66.7%) | |
| | High | 0 (0.0%) | 1 (14.3%) | 0 (0.0%) | 0 (0.0%) | 1 (16.7%) | 0 (0.0%) | |
| | Heterogeneous | 2 (50.0%) | 0 (0.0%) | 0 (0.0%) | 8 (40.0%) | 1 (16.7%) | 0 (0.0%) | |
| **T2 signal** | Low | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (16.7%) | 0 (0.0%) | **0.02** |
| | ISO | 0 (0.0%) | 4 (57.1%) | 4 (80.0%) | 1 (5.0%) | 1 (16.7%) | 0 (0.0%) | |
| | High | 1 (25.0%) | 1 (14.3%) | 0 (0.0%) | 4 (20.0%) | 1 (16.7%) | 1 (33.3%) | |
| | Heterogeneous | 3 (75.0%) | 2 (28.6%) | 1 (20.0%) | 15 (75.0%) | 3 (50.0%) | 2 (66.7%) | |
| **DWI** | Restricted | 1 (25.0%) | 4 (57.1%) | 3 (60.0%) | 14 (70.0%) | 4 (66.7%) | 1 (33.3%) | 0.5 |
| | W/O restriction | 3 (75.0%) | 3 (42.9%) | 2 (40.0%) | 6 (30.0%) | 2 (33.3%) | 2 (66.7%) | |
| **Enhancement** | Homogeneous | 0 (0.0%) | 3 (42.9%) | 2 (40.0%) | 6 (30.0%) | 1 (16.7%) | 1 (33.3%) | 0.6 |
| | Heterogeneous | 3 (75.0%) | 3 (42.9%) | 3 (60.0%) | 13 (65.0%) | 3 (50.0%) | 2 (66.7%) | |
| | Peripheral | 1 (25.0%) | 1 (14.3%) | 0 (0.0%) | 1 (5.0%) | 2 (33.3%) | 0 (0.0%) | |

**Table 5.** Relationship between hormonal secretion with ADC, and tumor sizes.

| | Pathology | | | | | | |
|---|---|---|---|---|---|---|---|
| | **PRL** | **GH** | **PRL+GH** | **FSH/LH** | **Nullcell** | **Invasive** | **P-value** |
| **ADC** | 1321 ± 823.76 | 774 ± 441.61 | 586 ± 292.24 | 766.1 ± 479.49 | 1022.33 ± 811.47 | 610 ± 549.21 | 0.3 |
| **Length** | 38.75 ± 23.29 | 20.29 ± 8.79 | 24.2 ± 18.21 | 29.55 ± 8.07 | 21.83 ± 4.02 | 31.67 ± 4.04 | 0.09 |
| **Width** | 43.75 ± 25.81 | 18.14 ± 9.96 | 17.6 ± 8.56 | 24.45 ± 6.32 | 20.83 ± 6.43 | 35.33 ± 11.15 | **0.002** |
| **Height** | 34.75 ± 24.68 | 18.29 ± 8.1 | 19.6 ± 11.93 | 30.95 ± 9.98 | 23.83 ± 11.37 | 31 ± 9.54 | 0.08 |

No significant differences were observed between other pathologic findings regarding age (P-values>0.05).

Significant differences in tumor volume were observed between prolactin (PRL) and growth hormone (GH) groups (p=0.002), PRL and Follicle-stimulating hormone (FSH). Luteinizing hormone (LH) groups (p=0.003), and PRL and Nullcell groups (p=0.004) with the larger tumors in the PRL group. There was no association between hormonal status and sexes (all P-values>0.05). Age and tumor volume were not associated (P-value> 0.131).

We evaluated the level of Ki67 in macroadenomas, and the mean level was 2.5±1.8%. There was no association between MRI findings and Ki67 level, but the difference in tumor volume between Ki67 groups (1-3% vs. more than 3%) was significant (P-value: 0.012), and tumor volume was greater if Ki67 was higher than 3%.

## Discussion

In this study, which was conducted to evaluate the relationship between multiparametric MRI findings, pathological features, and type of secreting hormones in patients with pituitary macroadenoma, forty-five

patients were evaluated. The mean age was 48.22±14.58 years, and 55.6% of the patients were male. The average age of patients in the null cell group was significantly older than the PRL group, which may be attributed to several reasons like hormone secretion in prolactinomas causing noticeable symptoms versus null cell tumors without secretion whose symptoms appear large enough to compress surrounding structures. Furthermore, the growth rate in prolactinomas is higher than in null cell tumors due to disrupted hormonal feedback mechanisms and dopamine resistance, so it takes more time for null cell tumors to become large enough to cause symptoms.

Regarding MRI sequences, most patients (48.9%) had isointense lesion in T1W and most patients (57.8%) had heterogeneous signals in T2W. The signal heterogenicity in T2W may be due to larger tumors in this study compared to microadenomas. Invasion to the Infrasellar space is the most common finding between local extension of masses. However, the most common site of invasion in the FSH-LH group is the 3rd ventricle (70%), which may help us to predict hormonal secretion of tumors using MR imaging. Tumors signal on T2 were statistically remarkable in the FSH-LH group (75% heterogenous on T2). The mean width was significantly higher in the PRL group and was the lowest in PRL+GH. The mean tumor size in the PRL group was significantly higher than other types.

In some papers, direct signal intensity of adenoma was compared with pathologic results, but even with the same scanning parameters, signal intensity of the same parts of the brain in different patients is variable. According to Wei et al's study, pons' signal intensity on the bridge arm level is stable and homogenous on axial MRI. As a result, we used pontine ADC as a reference and calculated tumor to pontine ADC ratio. The mentioned study was conducted to compare MRI and pathological results to assess the relationship between pituitary adenoma and tumor consistency. There was a significant difference between the collagen content of different tumors. It was concluded that the signal intensity of the tumor on T2WI and ADC images has predictive value for pituitary adenoma consistency, and T2WI is more reliable[13-16]. Additionally, in other studies adenoma-to-middle cerebellar peduncle ratio is a good screening tool for consistency detection in adenoma. Ratio > 1.8 has a high predictive value for soft consistency adenoma. A ratio <1.5 has a high predictive value for firm consistency adenomas[17]. In the current study, it was found that most of the patients (57.8%) had heterogenous signals on T2W, which may be due to the larger size of macroadenomas and their susceptibility to cystic degeneration, hemorrhage, and necrosis. There is also a significant relationship between hormonal secretion of tumors and T2 signal in our study, and most of the FSH-LH secreting tumors have heterogenous signal on T2 but this relationship was not seen with T1W. Additionally, there is no correlation between tumor-to-pons mean ADC ratio and hormonal secretion and cellular subtype. However, this study did not evaluate the correlation of tumor consistency with adenoma to pontine ADC ratio.

Yiping et al. evaluated the role of BLADE imaging (MR) and other traditional MRI parameters in predicting pituitary adenoma consistency in combination with pathological results. Thirty four patients post-surgery with a pathological diagnosis of pituitary adenoma were included in the study. Twenty-nine pituitary adenomas were considered soft, and the rest as hard. The SI ratio of T1-weighted images before or after enhancement, T2-weighted images, or ADC values showed no significant correlation with adenoma consistency. Partially, the ADC value is diagnostic for predicting strict adherence for ADC <1.077.ADC value showed a close relationship with collagen content, and lower ADC value was associated with increased collagen content[14]. In our study, the collagen content of the tumor tissue was not investigated. However, it was seen that ADC had no significant relationship with the cellular and hormonal contents of tumors. In fact, ADC has no diagnostic value in MRI for prediction of the pathological type of tumor and hormone secretion[18].

The results regarding the impact of tumor size with subtypes of pituitary adenomas are different based on secreted hormones. For example, in a study, it was seen that there was no relationship between age, sex, and tumor size with the type of adenoma based on secreted hormone[19]. However, in another study, it was seen that the tumor size in non-functioning adenomas with adrenocorticotrophic hormone (ACTH), GH, and LH were negatively correlated. Tumor size of somatotropic adenomas was positively correlated with GH but

negatively correlated with male testosterone. Prolactinoma tumor size was positively correlated with prolactin level[20]. There was a significant difference in age between the null cell and PRL groups, and the mean age of patients in the null cell group was approximately 26.67 years older than the PRL group. A significant difference in tumor volume was observed in comparing PRL with GH, FSH, LH, and Nullcell groups. The PRL-secreting tumors are significantly larger than GH, FSH-LH, and Null cell tumors. This may be due to disruption of hormonal feedback, genetic factors, dopamine resistance, or tumor biology in prolactinomas. The mean tumor volume significantly differed between Ki67 groups, 1 to 3%, versus Ki67 groups, which is more than 3%, which is considered the faster growth of tumors with upper amounts of Ki67. Considering the limitations of studies in this regard, it seems that more studies should be done in this field.

Evaluating macroadenomas with multiparametric MRI is beneficial for predicting tumoral behavior. As seen in our study, infra sellar extension is the most prevalent type of extension in macroadenomas. Even though the largest tumors are prolactinomas, gonadotroph pathology is suspected in tumors with invasion to the third ventricle. In older patients, null cell tumors are suggested. Also, in larger tumors, ki67 is higher, which causes rapid growth of the tumor and consequent deterioration of patient's situation.

## Conclusion

It is concluded that the most common pathological type of pituitary macroadenomas is FSH, LH, and the mean age at the diagnosis was 48 years. Extension to the infrasellar structures is the most common form of macroadenoma's local invasion. Heterogeneous signals on T2W and invasion to the third ventricle are more common in the FSH-LH group, and higher volumes of the tumor were observed primarily on PRL-secreting adenomas. Patients with null cell tumors were significantly older than the PRL form. Tumors with higher volumes had higher ki67.

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## Conflict of interest

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

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