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The Prognostic Roles of the Ki-67 Proliferation Index, P53 Expression, Mitotic Index, and Radiological Tumor Invasion in Pituitary Adenomas

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Abstract

The fourth edition of the World Health Organization (WHO) classification of pituitary tumors recommended evaluation of tumor proliferation and invasion to identify aggressiveness. We aimed to assess the prognostic roles of the Ki-67 proliferation index, mitotic index, P53 expression, and cavernous sinus invasion in pituitary adenomas (PAs). Among the 601 patients who underwent transnasal/transsphenoidal adenomectomy from 2001 to 2016, 101 patients (16.8%) who had tumors with a high (≥ 3%) Ki-67 index (group A) and a control group consisting of 43 patients with a low (< 3%) Ki 67 index who were matched for age, gender, and tumor type were included. Mitotic index and P53 expressions were evaluated. Patient characteristics, histopathology reports, pre/postoperative magnetic resonance imaging (MRI), and follow-up data were assessed retrospectively. The frequency of macroadenomas and mean tumor size were greater in group A when compared to group B (67.4 vs. 94.1%, $p< 0.01$ and 25 ± 10.6 vs. 18 ± 11 mm, $p< 0.01$, respectively). Invasion to cavernous sinus was found in 53 (36.8%) patients and was more frequent in group A ($p<0.01$). The mean number of surgery was higher in group A than group B ($p< 0.05$). The mean follow-up period was 46.6 ± 34 months. The postoperative MRIs and follow-up data for at least 24 months were available in 117 patients. Recurrence risk was higher in group A than group B ($p = 0.03$). Tumors with high Ki-67 proliferation index were grouped as 3–5, 6–10, 11–15, and > 15%. The risk of recurrence was not different between groups of high Ki-67 index. The optimal cutoff point of the Ki-67 proliferation index that predicted recurrence was 2.5% with 84.6% sensitivity and 47.4% specificity. The cavernous sinus invasion on MRI was associated with recurrence ($p = 0.03$). Tumor size and recurrence risk were not associated with P53 expression. High P53 expression was related with cavernous sinus invasion ($p = 0.03$). The mitotic index was not associated with recurrence risk and tumor invasion. Recurrence risk was higher in tumors with ≥ 2 histopathological atypia criteria ($p = 0.01$). High Ki-67 index with a 2.5% cutoff point and cavernous sinus invasion on MRI are reliable markers for predicting recurrence in PAs. Recurrence risk is also higher in tumors with two histopathological aggressiveness criteria. Strict follow-up and more aggressive treatment approaches may be necessary for invasive-proliferative PAs.

Keywords Pituitary adenoma · Recurrence risk · Ki-67 · P53 · Mitotic index · Cavernous sinus invasion

Introduction

The term ″aggressive pituitary adenoma″ refers to tumors characterized by invasion to adjacent tissues and recurrence and resistance to conventional treatment strategies [1–3]. A classification including the subgroup “atypical pituitary adenoma” (APA) was proposed by the World Health Organization in 2004 [4]. This description involved pituitary tumors with morphological features of invasive growth, increased mitotic index, extensive nuclear staining of P53 and Ki67 (MIB-1) proliferation index greater than 3% [4]. Presence of atypical histopathological features was suggested as an independent risk factor for tumor aggressiveness [5]. However, atypical adenomas did not match up with aggressive adenomas consistently [2, 6]. The results of the previous studies which investigated the efficiency of “atypical histopathological features,” defined by the WHO (2004) in predicting aggressive PAs, demonstrated controversial results. The new edition of the WHO classification (4th edition, 2017) of

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endocrine tumors did not include the "atypical adenoma" term, but recommended evaluation of the Ki-67 proliferation index, mitotic index, and radiological/surgical evidence of invasion to predict aggressive behavior [7]. Routine evaluation of P53 expression was not recommended in the new edition. Previous studies suggested variable thresholds of the Ki-67 proliferation index to predict recurrence [8, 9]. However, no specific cutoff values for Ki-67 and mitotic indexes were mentioned in the 2017 WHO classification of pituitary tumors [7].

In the present study, we aimed to assess the impact of the Ki-67 proliferation index, P53 expression, mitotic index, and cavernous sinus invasion on recurrence of PAs.

Materials and Methods

Patients

Among 601 patients who underwent transnasal/transsphenoidal (TN-TS) adenomectomy in Ankara University Faculty of Medicine, from 2001 to 2015, 101 patients (16.8%) who had tumors with Ki-67 labeling index greater than or equal to 3% were included and categorized as group A. The control group (group B) consisted of 43 patients matched for age, gender, and tumor type but had a Ki-67 index lower than 3%. Demographical characteristics, histopathology reports, pre/postoperative radiological findings, tumor type, and recurrence of tumors were assessed retrospectively. Patients who received medical treatment or radiotherapy prior to surgery were excluded from the study.

Cavernous sinus invasion on magnetic resonance imaging (MRI) was considered as grades 2–4 according to Knosp's classification [3, 10].

Follow-up data of patients whose medical records were available for at least 24 months was evaluated to determine disease status. Recurrence was defined as a newly identified tumor after total resection or enlargement of a remnant during follow-up or proven hormonal relapse of secretory PAs. The study was approved by local Ethical Committee of Ankara University Faculty of Medicine (April, 2016, 07-296-16).

Immunohistochemistry

Hematoxylin and eosin (H&E)-stained slides of the tumor samples were re-evaluated and the diagnosis was confirmed by two pathologists (SK, EE). For each case, a representative block was determined to use for both mitotic count index and immunohistochemical evaluation. Sections with 4-μm thickness were incubated with p53 (clone DO-7, Ventana) antibodies, in an automatic immunostainer (BenchMark XT Staining Module, Ventana Medical Systems Inc.; Tucson, AZ, USA) using the streptavidin Biotin complex immunodetection system. Antigen retrieval was achieved by CC1 (EDTA) solutions (Ventana) and protein blockage was applied. Diamino benzidine was used for chromogen and followed by hematoxylin counterstaining. The Ki-67 labeling indexes of tumors which were already performed (clone SP6, Cell Marque, 1:200 dilution) at the time of diagnosis were assessed retrospectively (Fig. 1).

As suggested by other authors, mitotic counts were performed by reviewing at least 20 high-power microscopic fields at × 400 objective (1.8 mm^2), beginning from the first mitosis identified, and the rate of Ki67 (MIB1) and p53 were evaluated as the maximum percentage of positive nuclei by counting at least 1000 tumor cells [11].

Immunohistochemical analysis of P53 was performed in tumor tissues of 80 patients who had appropriate paraffin-embedded tissues for demonstration of histological characteristics of tumors. The mitotic index was evaluated in tumor tissues of 85 patients who had appropriate paraffin-embedded tissues (Fig. 2).

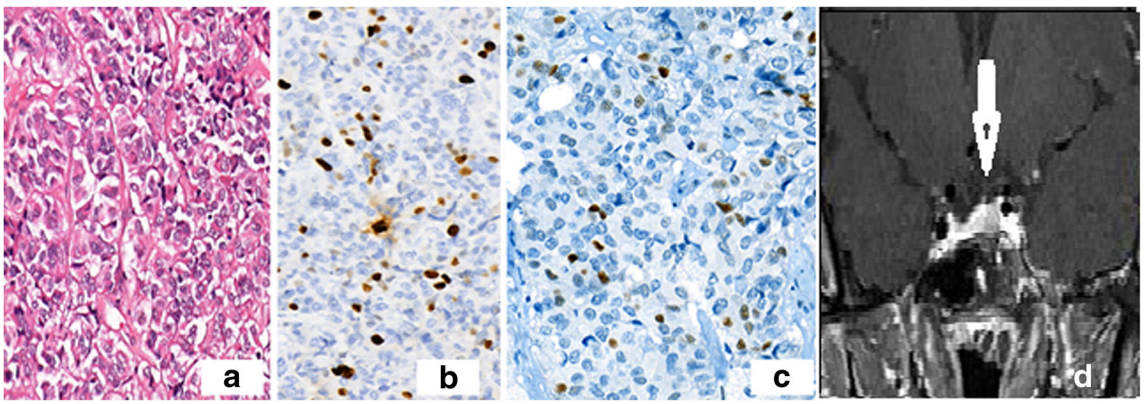

Fig. 1 **a** A pituitary adenoma showing large eosinophilic cells with abundant cytoplasm (hematoxylin & eosin, × 400). **b** High Ki-67 proliferation index (5% was noted). **c** Tumor cells showing P53 expression (22% was noted). **d** Pituitary MRI (T1 weighted coronal) showing a milimetric recurrent GH-secreting pituitary lesion on the left side of the pituitary gland

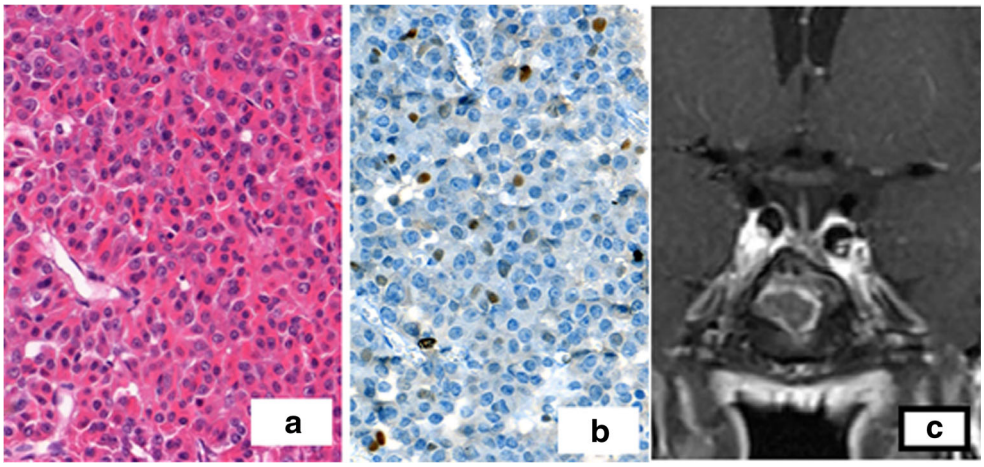

Fig. 2 a A pituitary adenoma with uniform nuclear morphology (hematoxylin & eosin, × 400). **b** Expression of P53 in tumor cells noted as 35% (immunohistochemistry, × 400). **c** Pituitary MRI (T1 weighted coronal) of a patient with acromegaly, showing only postoperative changes at the sixth year of follow-up

Overexpression of P53 was defined as 20% or more immunoreactivity in tumor cells with reference to a former study [12].

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 20.0 (IBM Corp, NY, USA). Categorical data were compared using the chi-square Fisher exact test. Group data with a normal distribution were compared using the Student *t* test or analysis of variance, and nonparametric data were compared using the Mann-Whitney *U* or Kruskal-Wallis test. Values were expressed as mean ± standard deviation or median as appropriate. The Spearman correlation test was used for continuous variables without normal distribution. The Pearson correlation test was used for continuous variables with normal distribution. Receiver operating characteristic (ROC) analysis was performed to determine the cutoff scores.

Results

Among 601 patients who underwent the TN/TS adenomectomy procedure for the treatment of PA, the frequency of tumors with a high Ki-67 labeling index (≥ 3) was 16.8% ($n = 101$).

The demographic and clinicopathologic characteristics of patients/tumors were summarized in Table 1. The most frequent symptom was visual disturbance ($n = 50$, 34.7%) followed by headache ($n = 32$, 22.2%) and loss of menstrual periods in women/erectile dysfunction in men ($n = 32$, 22.2%). Invasion to the cavernous sinus was found in 53 (36.8%) patients (Table 1).

Mean long axis diameter of adenoma was higher in group A when compared to group B (25 ± 10.6 vs.18 ± 11 mm, $p < 0.01$). The frequency of macroadenomas and

Table 1 The demographic, clinicopathological, and radiological characteristics of patients/tumors

Gender	
Male, *n* (%)	74 (51.4)
Female, *n* (%)	70 (48.6)
Age at diagnosis (years), mean ± SD	46.9 ± 12.7
Follow-up period (months), mean ± SD	46.6 ± 34
Tumor type;	
Somatotroph, *n* (%)	51 (35.4)
Lactotroph, *n* (%)	29 (20.1)
Gonadotroph, *n* (%)	23 (16.0)
Corticotroph, *n* (%)	18 (12.5)
Thyrotroph, *n* (%)	4 (2.8)
Plurihormonal, *n* (%)	2 (1.4)
Null cell, *n* (%)	17 (11.8)
Preoperative optic nerve/chiasm compression, *n* (%)	41 (28.5)
Preoperative central hypothyroidism, *n* (%)	31 (21.5)
Preoperative secondary adrenal insufficiency, *n* (%)	27 (18.9)
Preoperative secondary hypogonadism, *n* (%)	16 (11.1)
Preoperative panhypopituitarism, *n* (%)	4 (2.8)
Recurrence[a]	
Present, *n* (%)	39 (33.3)
Absent, *n* (%)	78 (66.7)
Tumor size (maximum diameter), mean ± SD	23.3 ± 11.4
Macroadenoma, *n* (%)	20 (13.9)
Microadenoma, *n* (%)	124 (86.1)
Cavernous sinus invasion on MRI, *n* (%)	53 (36.8)
Number of surgical procedures, median (min-max)	1 (1–5)
Number of patients who received radiotherapy, *n* (%)	2 (1.7)
Number of patients who received gamma-knife, *n* (%)	10 (8.5)

ACTH adrenocorticotropic hormone, *MRI* magnetic resonance imaging, *TSH* thyrotrophin-stimulating hormone

[a] Recurrence was evaluated in 117 patients who were followed up for at least 12 months and had postoperative MRI and hormonal evaluations

invasion on MRI was higher in group A compared to group B (67.4 vs. 94.1%, $p < 0.01$) (Table 2). Frequency of an increased mitotic index was not different between groups ($p = 0.2$). Clinical and histopathological features of patients and tumors according to Ki-67 proliferation index groups are summarized in Table 2.

Postoperative residual tumor was observed on MRI in 43% ($n = 62$) of patients. Frequency of residual tumor was not different between study groups. The median number of operations was higher in group A when compared to group B [median = 1 (min-max = 1–5) vs. median = 1 (min-max = 1–2), $p = 0.002$]. In the tumor tissue of patients who received conventional radiotherapy ($n = 2$) or gamma-knife ($n = 10$), the Ki-67 proliferation index was ≥ 3 in specimens of first surgery.

Follow-up data was available in 117 patients (more than 24 months after surgery). Mean follow-up period was 49.7 ± 31.1 months. Recurrence was more frequent in group A ($p < 0.01$) (Table 2). When group A was categorized according to Ki-67 indices as 3–5%, 6–10, 11–15, and > 15%, there was no difference between groups regarding the risk of recurrence. The cutoff value of the Ki-67 labeling index predicting recurrence was 2.5% with 84.6% sensitivity, 47.4% specificity, 44.5% PPV, and 86.1% NPV (AUC = 0.63, 95% CI 53–73%).

Recurrence of tumor was found in 39 (33.3%) patients among 117 patients whose follow-up data was available for at least 24 months. Recurrence was more frequent in PAs with cavernous sinus invasion ($p = 0.03$). Clinical and histopathological features of tumors according to presence of recurrence are summarized in Table 3.

Tumor size and recurrence were not associated with P53 expression ($p = 0.4$ and $p = 0.2$, respectively). Cavernous sinus invasion was positively associated with P53 expression [median 0 (min-max = 0–35) vs. 6 (8–60), $p = 0.02$]. When tumors were categorized as p53 expression ≥ 20% ($n = 8$) and < 20% ($n = 72$), no association was observed between overexpression and tumor recurrence.

The mitotic index was positively associated with presence of macroadenoma ($p < 0.05$). Recurrence and invasion on MRI were not associated with the mitotic index.

Presence of two or more histopathological atypia criteria was observed in 24 tumors and recurrence risk was higher in these tumors ($p < 0.01$).

Table 2 Clinical and histopathological features of adenomas in groups A and B

	Group A	Group B	*P*
Age at diagnosis (years), mean ± SD	40.5 ± 12.2	42.6 ± 13.2	0.34
Follow-up period (months), mean ± SD	48.9 ± 34.3	51.3 ± 25.2	0.69
Tumor type			
Secretory			0.3
Somatotroph, *n* (%)	37 (36.6)	14 (32.6)	
Lactotroph, *n* (%)	22 (21.8)	7 (16.3)	
Gonadotroph, *n* (%)	15 (14.9)	8 (18.6)	
Corticotroph, *n* (%)	9 (8.8)	9 (20.8)	
Thyrotroph, *n* (%)	2 (2)	2 (4.7)	
Plurihormonal, *n* (%)	2 (2)	0 (0)	
Null cell *n* (%)	14 (13.9)	3 (7)	
Tumor size (maximum diameter), mean ± SD	25 ± 10.6	18 ± 11	< 0.01
Macroadenoma, *n* (%)	95 (94.1)	29 (67.4)	< 0.01
Microadenoma, *n* (%)	6 (5.9)	14 (32.6)	
Invasion on pituitary MRI, *n* (%)	46 (45.5)	7 (16.2)	< 0.01
Preoperative optic nerve/chiasm compression, *n* (%)	38 (57.6)	3 (7.3)	< 0.01
Preoperative central hypothyroidism, *n* (%)	24 (32.4)	7 (16.3)	0.057
Preoperative secondary adrenal insufficiency, *n* (%)	16 (21.6)	11 (25.6)	0.6
Preoperative secondary hypogonadism, *n* (%)	10 (13.5)	6 (14)	0.94
Preoperative panhypopituitarism, *n* (%)	3 (4.1)	1 (2.3)	0.62
Increased mitotic index[a], *n* (%)	26 (60.5)	22 (52.4)	0.27
P53 expression, median (min-max)	0 (0–30)	7 (0–60)	< 0.01
Recurrence[b], *n* (%)	33 (44.6)	6 (14.0)	< 0.01

[a] Mitotic index and P53 expression were evaluated in tumor tissues of 85 and 80 patients who had adequate specimens for re-evaluation, respectively

[b] Recurrence was evaluated in 117 patients whose follow-up data was available for at least 24 months

Table 3 Clinical and histopathological features of patients and tumors according to presence of recurrence

	Tumors with recurrence ($n = 39$)	Tumors without recurrence ($n = 78$)	p
Age at diagnosis (years), mean ± SD	39.5 ± 11.9	41.5 ± 13.2	0.38
Gender, M/F, *n* (%)	21/18	41/37	0.89
Tumor type			
Somatotroph, *n* (%)	12 (30.8)	27 (34.6)	0.1
Lactotroph, *n* (%)	4 (10.3)	18 (23.1)	
Gonadotroph, *n* (%)	8 (20.5)	14 (18.0)	
Corticotroph, *n* (%)	8 (20.5)	9 (11.5)	
Thyrotroph, *n* (%)	0 (0)	4 (5.1)	
Plurihormonal, *n* (%)	2 (5.1)	0 (0)	
Null cell, *n* (%)	5 (12.8)	6 (7.7)	
Tumor size (maximum diameter), mean ± SD	25.8 ± 11.9	21.9 ± 11.1	0.15
Macroadenoma, *n* (%)	34 (87.2)	65 (83.3)	0.5
Microadenoma, *n* (%)	5 (12.2)	13 (16.7)	
Cavernous sinus invasion on pituitary MRI, *n* (%)	28 (71.8)	25 (32.1)	< 0.01
Ki-67 proliferation index, median (min-max)	4 (1–20)	3 (1–30)	< 0.01
< 3, *n* (%)	6 (15.4)	37 (47.4)	< 0.01
≥ 3, *n* (%)	33 (84.6)	41 (52.6)	
P53 expression[a], median (min-max)	6 (0–60)	0 (0–35)	0.2
< 20, *n* (%)	28 (90.3)	44 (89.8)	0.9
≥ 20, *n* (%)	3 (9.7)	5 (10.2)	
Mitotic index[b], median (min-max)	2 (1–10)	2 (1–8)	0.24
< 2, *n* (%)	12 (38.7)	24 (46.2)	0.5
≥ 2, *n* (%)	19 (61.3)	28 (53.8)	

[a] P53 expression was available in 80 patients with follow-up data

[b] Mitotic count was available in 83 patients with follow-up data

Microscopic dural invasion was not noted in any of the PAs evaluated in this study.

Discussion

In the present study, we observed that a high Ki-67 proliferation index had predictive value for recurrence in pituitary adenomas. Tumor size, presence of macroadenoma, and invasion on pituitary MRI were higher in tumors with a high Ki-67 proliferation index. The mitotic index and expression of P53 were not associated with recurrence risk. However, presence of any two of histopathological aggressiveness criteria was associated with recurrence.

The data regarding the relationship between the Ki-67 proliferation index, invasiveness and recurrence of PAs has been debated [13]. In a retrospective study, Zaidi et al. reported that size of tumor, cavernous sinus invasion on MRI, and a high Ki-67 proliferation index were significantly associated with tumor aggressiveness [2]. Chiloiro et al. evaluated 343 untreated PAs and categorized tumors according to a 1.5% cutoff value of the Ki-67 proliferation index as stated in their former study [6, 9]. The authors reported that a Ki-67 index ≥ 1.5 was associated with higher risk of sphenoid/cavernous sinus invasion on MRI and recurrence [6]. However, no difference was found between typical and atypical PAs regarding the risk of recurrence. In the study of Del Basso De Caro, the Ki-67 proliferation index was not found to be related with the risk of aggressiveness or invasiveness of atypical PAs [14]. Zakir et al. reported that the Ki-67 proliferation index was not associated with tumor progression in giant PAs [15]. In the study of Kim et al., a Ki-67 index higher than 3% and presence of two atypical features were associated with recurrence in PAs [12]. Recently, Raverot et al. classified pituitary adenomas into five grades according to cavernous sinus invasion and proliferation markers, and showed that their classification system predicted risk of early recurrence or progression [16]. Our results were consistent with former reports which suggested a significant relationship between recurrence risk and a high Ki-67 proliferation index [2, 12].

In addition, previous reports revealed conflicting results in terms of the relationship between tumor size and the Ki-67 proliferation index [2, 17]. We showed that the Ki-67 proliferation index was positively associated with the tumor size and frequency of macroadenoma, in concordance with the study of Zaidi et al. [2].

The cutoff value of the Ki-67 proliferation index which predicted recurrence risk varied between former studies [6, 8, 18, 19]. Discrepancies between results were explained by different methodologies of Ki-67 counting [18]. In the present study, we classified PAs in two groups according to the WHO 2004 classification. The cutoff value of the Ki-67 index which predicted recurrence was 2.5% in our series.

Invasion of PA was not well-defined in previous WHO criteria. Neuroradiological, histopathological, and intraoperative observations of invasion were all separately regarded as invasion criteria. In our series, microscopic dural invasion was not noted in any of the PAs. However, this finding may be related with insufficient collection of specimens for evaluation of invasion during surgery. We did not use intraoperative observation as criteria of invasion, as it was a subjective method and operative reports were occasionally insufficient to exclude invasion. Cavernous sinus invasion on MRI was shown to be a reliable factor in predicting prognosis [20]. High Knosp grade was found to be an independent risk factor for recurrence [3]. Knosp grade 2 invasion on MRI was shown to increase the likelihood of surgically proven invasion and to be associated with worse disease-free survival [9, 10]. Therefore, we defined invasion as grade 2–4 Knosp score on MRI. We observed that invasion to cavernous sinus on MRI was associated with recurrence risk.

The relationship between increased proliferation and invasiveness of PAs remains controversial [13, 21, 22]. In the study of Chacko et al., the Ki-67 index was significantly higher in tumors with cavernous sinus invasion [20]. We showed that cavernous sinus invasion was significantly frequent in tumors with a ≥ 3% Ki-67 proliferation index. Also, P53 expression was positively associated with radiological invasion. Our results confirmed that proliferation markers were predictors of invasive tumor growth.

In the present study, recurrence risk was associated with neither the mitotic index nor p53 expression. The data about the role of P53 overexpression to predict recurrence in PAs was controversial and no consensus was available for specific cutoff values [23–25]. Ozer et al. reported that P53 positivity was associated with recurrence in PAs [24]. Another study evaluated p53 expression in giant PAs, and found association between tumor progression and P53 overexpression [15]. However, Oliveira et al. observed low frequency of P53 positivity among invasive PAs and suggested that P53 was not useful for predicting aggressiveness [25]. In a recent study, Del Basso De Car evaluated 50 patients with atypical PAs and showed that no association was found between P53 overexpression and invasiveness/aggressiveness of these tumors [14]. However, staining methods and definition of overexpression varied between previous studies [15, 24, 25]. Oliveira et al. defined P53 positivity as the presence of at least a group of stained cell nuclei, whereas Del Basso De Caro et al. defined > 10% staining as overexpression [14, 25]. In the study of Hadzhiyanev et al., p53 expression was evaluated in three categories semi-quantitatively [26]. The authors defined moderate to severe expression as approximately 50% positive cells and expression in most of the cells, respectively. No association was found between p53 expression, clinical features, and prognosis, whereas the Ki-67 labeling index was positively related with P53 expression [26]. In the study of Kim et al., P53 overexpression was defined as nuclear reactivity of 20% or more in tumor cells [12]. Their results revealed that overexpression was related with tumor recurrence [12]. In our series, tumor size and recurrence were not associated with P53 expression. Invasion to adjacent tissues on MRI was positively associated with P53 expression. Median percentage of P53 expression was higher in the PA group with a high Ki-67 labeling index. When P53 expression equal to or greater than 20% was considered as overexpression according to previous report of Kim et al., no association was found between P53 and recurrence risk [12].

The prognostic role of the mitotic index in PAs has been debated. Previously, Miermeister et al. reported that a mitotic index equal to or greater than 2/10 HPF was associated with recurrence [27]. In the study of Lee et al., the authors did not find any prognostic significance of the mitotic index in PAs [28]. Consistently, the mitotic index was not found to be associated with recurrence risk and invasiveness in our study.

The major limitation of our study was its retrospective design.

In conclusion; we showed that a high Ki-67 index and cavernous sinus invasion on MRI were reliable markers for predicting recurrence in pituitary adenomas. The cutoff value of the Ki-67 index that predicted worse outcome was 2.5%. A high Ki-67 index was also associated with greater tumor size and radiological invasion. Increased expression of P53 was associated with cavernous sinus invasion. Recurrence risk was higher in tumors with two histopathological atypia criteria. Cavernous sinus invasion and a high Ki-67 proliferation index together may be used as a predictor of aggressive tumor behavior. Strict follow-up and multimodal treatment approaches may be necessary for invasive-proliferative pituitary adenomas.

Compliance with Ethical Standards

The study was approved by local Ethical Committee of Ankara University Faculty of Medicine (April, 2016, 07-296-16).

Conflict of Interests The authors declare that they have no conflict of interests.

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