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RESULTS OF THE INTEGRATED RISK ANALYSISRECURRENCE OF GROWTH OF INACTIVE PITUITARY ADENOMAS IN THE POSTOPERATIVE PERIOD

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Abstract

The aim of the study was to perform an integrated analysis of risk factors for recurrence of non-functional pituitary adenomas (NFPA) in the postoperative period.

Materials and methods of the study. We studied 20 patients with NFPA (group 1 - 10 pituitary macroadenomas and group 2 - 10 giant pituitary adenomas) who underwent transnasal pituitary adenomectomy.

All patients underwent examinations, including fundus examination, visual field measurement every 3 months, studies of the levels of STH, IGF-1, LH, FSH, ACTH, TSH, prolactin, free thyroxine, cortisol, as well as immunohistochemical studies of operated patients to determine the levels of Ki67, p53 expression.

Results.The analysis showed that the most valuable predictors of tumor recurrence in NFPA are the Ki-67 labeling index ≥4% (OR = 3.67), brain invasion (3.34), suprasellar invasion (OR = 3.24), and disease duration (2.95). Genetic predisposition is also significant in the development of tumor recurrence. The frequency of the hereditary factor for NAG is 78.78% (OR = 2.51).

Conclusions. 1. The immunohistochemical (IHC) studies showed a significant correlation between the Ki-67 marker, tumor size, and invasiveness in both groups. This marker should be used as a prognostic criterion for recurrence of growth and invasive growth of NFPA Using logistic regression analysis (LRA), we were able to show that all four criteria (Ki-67 ($p < 0.001$); OR 5.2 // p53 ($p < 0.001$); OR 2.1 // invasiveness ($p < 0.001$); OR 8.2)) were significant for the group with giant NAG and a reliable correlation was found between them ($p < 0.001$).

Keywords: NFPA, IHC, proliferation markers, correlation.

Introduction

Although the diagnosis of atypical pituitary adenoma was introduced by the World Health Organization (WHO) over a decade ago, specific cutoff values for the criteria of "increased mitotic index" and "extensive nuclear staining for p53 immunoreactivity" remain lacking. They are also lacking for determining the behavior of NFPA s in early stages to determine the potential size, invasiveness, degree of aggressiveness, and metastatic potential of the tumor. Therefore, the first important aspect of the study

presented here was to propose reliable, reproducible, and easily predictable cutoff values for the mitotic rate and p53 expression level, the most readily available marker.

Thus, nuclear accumulation of p53 as a prognostic marker of pituitary tumors is discussed in the literature in various areas. There are several studies with different results regarding its importance in behavior growth (aggressive/invasive) adenomas [1;2]. For atypical pituitary adenomas, German authors in 2015 proposed using a threshold value for p53 ≥2% of clearly immunoreactive nuclei.

Very high specificity (97%) and sensitivity (95%) indeed indicate that the proliferation index is a very good and reliable diagnostic tool (Youden index 0.92), which provides important results for the diagnosis of NFPA aggressiveness. Compared with p53 immunoreactivity (0.94), Ki-67 had the highest CI (0.98), suggesting that it is the best single parameter for the diagnosis of NFPA aggressiveness, which is in line with previous publications. [3]. A total of 96% of cases were correctly classified by this single parameter alone. The probability of NFPA aggressiveness increases 5.2-fold per percentage of Ki67 immunoreactive nuclei ($p < 0.001$). A strong association between Ki-67, proliferation and adenoma recurrence status was confirmed in a recently published case-control study (n = 410) analyzing an eight-year postoperative follow-up period [4]. This and several subsequent studies proposed a classification system for pituitary adenomas according to tumor size, type, and a new grade of malignancy [5].

Invasive pituitary adenomas have been described as more aggressive in biological behavior and demonstrating an increased growth rate compared to non-invasive tumors [6]. However, 35 NFPA (23.2%) (n = 10/25) in our cohort showed an invasive growth pattern, which is consistent with several other observations published previously [7]. The low specificity reflects the fact that invasive growth is not limited to the giant NFPA group. According to our results, invasiveness was the least effective parameter for differentiating both adenoma subtypes. It showed a particularly wide confidence range. On the other hand, invasive growth remains a crucial prognostic factor in predicting patients' recurrence-free status and overall outcome [8].

The aim of the study is execute Integral analysis of risk factors for recurrence of inactive pituitary adenomas in the postoperative period.

Material and methods of research

We studied 20 patients with NFPA (Group 1 - 10 pituitary macroadenomas and Group 2 - 10 giant pituitary adenomas) who underwent transnasal pituitary adenomectomy. (TPA).The pituitary neurosurgery department of the Republican Specialized Scientific and Practical Medical Center of Endocrinology enrolled 12 patients between 2020 and 2022. Of these, 12 were men (60%) and 8 were women (40%). The average age of men was 48.12 years, while that of women was 46.15 years. The control group consisted of 10 healthy individuals with normal pituitary tissue.

The maximum mean tumor diameter determined by MRI diagnostics was 44.7 ± 13.6 mm in 10 patients with giant NFPA, and macroadenomas > 30 mm were present in 10 patients.

All patients underwent examinations, including fundus examination, visual field measurements every 3 months, studies of the levels of STH, IGF-1, LH, FSH, ACTH, TSH, prolactin, free thyroxine, cortisol, as well as immunohistochemical studies of operated patients with determination of the levels of Ki67

and p53 expression. In addition, the AKU scale was introduced for the first time (2022) to predict the degree of tumor removal in the preoperative period.

The patient's age at surgery, gender, and histopathological tumor parameters, such as the presence of nucleoli and invasiveness, and expression of the cell cycle markers p53 and Ki-67, were recorded. Only nuclei with distinct nuclear expression were considered. In cases of heterogeneity, a second and third assessment were performed. Verification of tumor invasion into surrounding anatomical structures (e.g., meninges, bone, brain tissue, sphenoid sinus) was assessed using surgical reports, preoperative MRI samples, or confirmed by definitive histological examination.

Proliferation markers Ki-67 and p53 were obtained semiquantitatively. Results were considered positive for cases with p53 ≥ 3+ (immunoexpression in 25 to 50% of cells), Ki-67 ≥ 2+ (immunoexpression in 10 to 25% of cells), and c-erbB2 ≥ 2+ (positivity in more than 10% of cells) according to local protocols. All samples were standardly fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin and PAS reactions.

We preferred to use a cutoff value of Ki-67 ≥ 4% for our cohort because it has better discriminatory power and is more accurately defined.

Statistical analysis

The obtained data were processed using Microsoft Excel and STATISTICA-6 software. The significance of differences in quantitative indicators (n> 12) was determined using the Wilcoxon signed-rank test for unrelated ranges; the nonparametric Fisher component randomization test for independent samples was used to determine the significance of small samples (n<12); and the Fisher-Irvine exact test was used for qualitative values. Differences between groups were considered statistically significant at P<0.05, correlation analysis was carried out using the nonparametric Spearman rank correlation method.

Results of the study.

Next, we performed a correlation between the markers Ki-67, p53 and demographic characteristics (Tables 1, 2).

Table 1. Correlation between the IHC marker Ki-67 and demographic characteristics of the groups

Indicators	Pearson's coefficient	1 group of macro NFPA, n=10		2nd group giant NFPA, n=10	
		Invasive growth	Non-invasive growth	Invasive growth	Non-invasive growth
Age	correlation	0.212	0.111	0.332	0.134
	r	0.527	0.98	0.432	0.453
Floor	correlation	0.169	0.119	-0.07	0.169
	r	0.612	0.587	0.87	0.812
Tumor size	correlation	0.58*	0.56*	0.67*	0.71*
	r	0.78	0.674	0.88	0.09

As can be seen from Table 1, a significant difference was found between the Ki-67 marker, tumor size and invasiveness in both groups.
As can be seen from Table 2, no significant difference was found between the p53 marker, tumor size, and invasiveness in both groups.
Thus, the IHC studies showed a significant correlation between the Ki-67 marker, tumor size, and invasiveness in both groups. This marker should be used as a prognostic criterion for recurrence and invasive growth of NFPA.
And finally, based on the completed studies of risk factors, we performed a mathematical prediction of the risk of recurrence of NFPA. growth in the postoperative period.
To determine the prognosis for the development of complications, we developed risk limits for tumor recurrence using the method of normalization of intensive indicators (NIP) proposed by E.N. Shigan [1983]. For this purpose, we created a table for accounting for possible risk factors.
This complex of assessed factors included: patient's gender, age, hereditary predisposition to oncology, presence of bad habits, duration of the disease, brain invasion, suprasellar invasion, retrosellar invasion, parasellar invasion, p53 labeling index ≥2%; Ki-67 labeling index ≥4%; panhypopituitarism (deficiency of more than 3 tropic hormones), tumor size more than 3 cm, brainstem symptoms, amaurosis, etc. Then, we calculated each risk factor using the relative risk (RR) indicator, which is the ratio of the maximum intensity level of the indicator to the minimum.

Table 2 Correlation between the IHC marker p53 and demographic characteristics of the groups

Indicators	**Pearson's coefficient**	**1 group of macro** NFPA., **n=10**		**2nd group giant** NFPA., **n=10**	
		Invasive growth	**Non-invasive growth**	**Invasive growth**	**Non-invasive growth**
Age	correlation	0.231	0.212	0.441	0.224
	r	0.654	0.87	0.512	0.564
Floor	correlation	0.109	0.121	0.09	0.134
	r	0.632	0.645	0.89	0.873
Tumor size	correlation	0.045	0.09	0.09	-0.8
	r	0.66	0.718	0.84	0.07

In addition, we calculated the normalized intensive index (NII) using the formula: NII = r/M, where: r is the intensive NII index per hundred examined individuals, M is the “normalizing index”.
For each parameter, additional odds ratios (OR) were calculated. “An odds ratio (OR) is a measure of the association between an exposure and an outcome. The OR represents the likelihood that an outcome will occur with a given exposure, compared with the likelihood that the outcome will occur in the absence of that exposure. Odds ratios are most commonly used in case-control studies [8;].” The pseudo coefficient of determination (Nagelkerkes R 2) was used to measure the predictive ability of the model. AUC (area under the curve) values were interpreted as follows: 0.5–0.7 = minimal; 0.7–0.9 = moderate; >0.9 = high discriminatory ability. Correlations between individual metric parameters (Ki-67, p53) were analyzed using Spearman’s rank correlation.
Data on the calculation of the integral assessment for tumor growth recurrence are presented in Table 3.

Table 3 Integral analysis of risk factors recurrence of tumor growth in the postoperative period

NFPA		%	NII	OR	IO	min	max
		59,8					
sex	men	56,78	0,972	**1,05**	1,02	1,03	1,09
	women	57,29	1, 123		1,04		
age	16-29 years old	43,01	0,783	**2,17**	1,46	1,65	3,48
	30-44 years old	61,43	0,971		2,43		
	45-59 years old	59,46	1,234		2,58		
	60-74 years old	79,18	1,786		3,45		
	S/S	63,42	0,825		1,72		
	N/S	58,12	1,287		1,46		
heredity for oncology	Eat	78,78	1,899	**2,21**	4,09	1,76	3,98
	No	82,33	1, 454		1,08		
brain invasion	Eat	87,12	2,875	**3,34**	2,99	1,08	3,95
	No	38,12	0, 145		1,06		
suprasellar invasion	Eat	79,83	3,762	**3,24**	3,98	1,78	3,98
	No	51,22	1,098		1,12		
retrosellar invasion	Eat	78,34	2,875	**1,43**	2,45	1,23	2,78
	No	43,23	1,234		1,12		
parasellar invasion	Eat	49,12	0,912	**1,07**	1,07	1,05	1,11
	No	51,33	1, 122		1,09		
p53 labeling index ≥2%;	Eat	69,98	2,998	**2,34**	4,06	1,09	3,67
	No	53,87	1,543		1,04		
Ki-67 labeling index ≥4%	Eat	88,24	3,078	**3,67**	4,76	1,23	3,98
	No	53,12	1,342		1,26		
bitemporal hemianopsia	Eat	68,71	0,865	**1,78**	1,05	1,06	2,09
	No	54,76	1,432		1,09		
panhypopituitarism	Eat	75,28	0,812	**2,19**	3,11	1,07	1,09
	No	55,21	1,544		1,07		
amaurosis	Eat	52,34	0,918	**1,67**	1,12	1,08	3,78
	No	50,45	1,155		1,07		
tumor size more than 3 cm	Eat	87,45	0,967	**2,56**	3,02	1,03	3,34
	No	54,23	1,454		1,05		
brainstem symptoms	Eat	76,45	0,823	**2,28**	3,02	1,03	3,09
	No	56,23	1,244		1,9		
duration of the disease	Up to 1 year	18,12	1,118	**2,95**	1,45	1,52	3,18
	1 - 5 years	39,23	0,865		3,12		
	6-10 years	78,27	1,765		5,23		
	10 years and above	89,27	1,287		3,22		

The analysis showed that the most valuable predictors of tumor recurrence in NFPA. are a Ki-67 labeling index ≥4% (OR = 3.67), brain invasion (OR = 3.34), suprasellar invasion (OR = 3.24), and disease duration (OR = 2.95). Genetic predisposition plays a significant role in the development of tumor recurrence. The frequency of the hereditary factor in NFPA. is 78.78% (OR = 2.51).

Based on a set of possible factors and the data from the calculations and tables, we determined the possible limits of risk values.

In this case, the risk limits are within the range of 19.76 - 44.59.

Thus, we calculated the probable risk limits for pituitary tumor recurrence (19.76 - 44.59), as well as the cutoff values. For this purpose, we divided the risk limits into three levels: low (up to 19.76), moderate (20.0 - 44.59), and high (45.0 or higher) risk of pituitary tumor recurrence.

The boundaries of the probability of the risk of tumor recurrence that we developed are presented in Table 4.

Next, having determined the total sum of the minimum and maximum scores for each risk factor, we developed a range of risk for the occurrence of tumor recurrence in patients with macro and giant NFPA.s:

1. The lowest score (for NFPA.: up to 19.76). Patients who achieve this score are considered to have a favorable prognosis and a low risk of tumor recurrence.
2. Intermediate - (for NFPA.: 20.0-44.59). Patients in this subrange are at higher risk of tumor recurrence and should be a focus of medical attention.
3. Highest - (for NFPA.: 45.0 or more). In this subrange, the influence of risk factors is greatest, and patients within this range have an unfavorable prognosis for tumor recurrence.

Table 4. Limits of the degree of probability of the risk of tumor recurrence

Subrange	**Subrange size**	**Subrange size**
	NFPA.	
Low probability	Up to 19, 76	Favorable prognosis
Average probability	20.0-44.59	Attention
High probability	45.0 and more	Poor prognosis

By using this technique, it is possible to optimize treatment and preventive measures to reduce the incidence of tumor recurrence in patients with macro and giant NFPA. in the postoperative period.

Using binary logistic regression analysis (LRA), it was confirmed that all four predictors (invasiveness, mitotic rate, p53, Ki-67) significantly contributed to the determination of the dependent variables (non-aggressive/aggressive adenoma). Correlation analysis showed that all four parameters considered were significant with each other at the 0.001 level. Only invasiveness and p53 were significant at the 0.05 level in relation to each other. This consistency of the four criteria of atypical tumor growth (i.e., Ki-67, invasiveness, mitotic rate, and p53 levels) was proposed by a number of authors, in particular by German authors Miermeister CP, Petersenn S et al. in 2015 for atypical pituitary adenomas [9, 10;].

In conclusion, our results showed that in all patients with giant pituitary adenomas, the absence of parasellar invasion was associated with a higher rate of tumor stability after treatment (p = 0.0389; Pearson residual = +3). However, parasellar invasion was not associated with the outcomes of tumor

regrowth/recurrence and cure/shrinkage. Infrasellar invasion and suprasellar extension were not considered good prognostic markers of clinical outcome. However, there was a tendency to associate the absence of extension into the third ventricle with a higher likelihood of tumor stability after treatment. Proliferative tumors, but mainly those classified as grade 2B (invasive-proliferative), showed a significant association with the rate of tumor regrowth/recurrence ($p = 0.0127$), confirming that these lesions should be considered as highly suspicious for neoplastic proliferation.

Conclusions

1. IHC studies showed a significant correlation between the Ki-67 marker, tumor size, and invasiveness in both groups. This marker should be used as a prognostic criterion for recurrence and invasive growth of NFPA.
2. Using logistic regression analysis (LRA), we were able to show that all four criteria (Ki-67 ($p < 0.001$); OR 5.2// p53 ($p < 0.001$); OR 2.1// invasiveness ($p < 0.001$); OR 8.2)) were significant for the group with giant NFPA. and a reliable correlation was found between them ($p < 0.001$).

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