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RESEARCH ARTICLE

PRACTICAL USE OF THE NEW 2017 WHO CLASSIFICATION OF SILENT PITUITARY ADENOMA; RETROSPECTIVE ANALYSIS IN SINGLE CENTRE

Hoon Gi Kim, Jinuk Kim, Gyuseo Jung, and *Young Zoon Kim

Department of Neurosurgery, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, South Korea

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ABSTRACT

Objective: To analyze the pathological and clinical features of silent pituitary adenoma (SPA) under the new 2017 World Health Organization(WHO) Classification of Tumors of Endocrine Organ, and to provide relevant experience for the clinical diagnosis and treatment of SPA. **Methods**: Under the new 2017 WHO Classification of Tumors of Endocrine Organ, histopathological features of silent pituitary adenoma were evaluated between 2018 and 2019 in single centre. **Results**: The medical records including radiological and histopathological reports of 220 patients (55.9% female, mean age 55.25±11.12 years) were retrospectively analyzed. Patients with visual field impairment, headache, and oculomotor palsy accounted for 59.5%, 37.7%, and 4.1%, respectively.9.5% of patients have evidence of apoplexy, the average maximum diameter of the tumor is 29.0±9.8mm, and the proportion of giant adenoma is 11.81%. The most common type of tumor is 107 cases of silent gonadotroph adenoma, followed by silent corticotroph adenoma 74 cases, 23 cases of null cell adenoma. Null cell adenoma is more invasive and Ki-67 index is higher (P<0.05). Three types of high-risk adenoma were identified, with 74 cases of silent corticotroph adenoma accounting for the highest proportion, followed by 4 cases of sparsely granulated somatotroph adenoma and 3 cases of PIT1-Positive Plurihormonal Adenomas. High-risk pituitary adenoma is higher than low-risk pituitary adenoma in invasive, recurrence and apoplexy (P<0.05). Invasive pituitary adenoma Ki-67 was significantly higher than non-invasive pituitary adenoma (P<0.001).The invasive of recurrent pituitary adenoma was higher than that of non-recurrent pituitary adenoma (P<0.05). **Conclusion**: The new version of the classification is very practical. Silent gonadotroph adenoma is the most common silent pituitary adenoma. High-risk pituitary adenoma, recurrent pituitary adenoma, and null cell adenoma have higher invasiveness and Ki-67 index.

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INTRODUCTION

Pituitary adenomas (PAs) according to the new 2017 World Health Organization (WHO)Endocrine Organ Tumor Classification (Lloyd, 2017) also known as pituitary neuroendocrine tumors (PitNets), are benign endocrine tumors that originate in the anterior pituitary gland. This tumor is currently the second most common intracranial tumor, with an incidence of about 7-41.3/10 million (Aflorei, 2014;Agustsson 2015), accounting for about 10% to 20% of common intracranial tumors(Daly, 2006).Under the new version of2017 WHO Endocrine Organ Tumor Classification, some pituitaryadenomas exhibit tumor mass effects and lack endocrine hormone-related symptoms. They are called clinically non-functional pituitary adenomas.

Corresponding author: **Young Zoon Kim,**
Department of Neurosurgery, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, South Korea.

For clinical symptoms related to the tumor mass effect, it usually appears only when the pituitary adenoma grows to a certain degree, and often shows behind the endocrine hormone-related symptoms, causing a delay in clinical diagnosis. According to estimates by other investigator, the average clinical diagnosis delay time is 1.96 ± 2.9 years (Knosp, 1993).Therefore, it has important clinical significance for the early identification of this adenoma.In terms of this clinical importance, there is a classification according to clinical presentation and classification according to transcription factors (Fig 1 A and B). Silent pituitary adenomas (SPA)are a pathological diagnosis, defined as the expression of one or more pituitary hormones and the corresponding pituitary transcription factor, but there is no evidence of excessive hormone secretion. Finally, there is no hormone expression, and no pituitary transcription factor positive immune response is called null cell adenoma. Under the new 2017 WHO classification, clinical non-functional pituitary adenomas, combined with transcription factor

immunohistochemistry, can be further classified as silent pituitary adenomas of the corresponding lineage. The research object of this study is the silent pituitary adenoma within the above definition. Although silent pituitary adenoma is more common in the clinic, there is still a lack of relevant research. This study retrospectively analyzed the clinical, biochemical, imaging and pathological characteristics of patients with silent pituitary adenoma under the guidance of the new edition of WHO Endocrine Organ Tumor Classification.

PATIENTS AND METHODS

Patient selection: Collect data from patients diagnosed with silent pituitary adenoma at the Department of Neurosurgery of our institute from2018 to 2019. All patients were treated with endoscopic endonasal and transsphenoidal surgery for pituitary adenoma. And those with incomplete laboratory tests andradiological data were excluded, and a total of220 patients were included as the research object (a total of 482 patients with pituitary adenoma treated by surgery during the same period).All subjects obtained the patient's informed consent before the study and signed a written informed consent agreement. The study was approved by the institutional review board of our hospital. All studies were conducted according to the guidelines of the Declaration of Helsinki for biomedical research. Informed consent was waived due to study's retrospective nature and minimal hazard to the participants.

Histopathological evaluation: Postoperative pathological tissue sections were fixed with formalin (37%) and embeddedinparaffin. Eachsection was analyzed using conventional immunohistochemical staining to detect the main pituitary hormones ofeach tissue and the pituitary transcription factor lineage (OriGene Technologies, Inc., antibody). The positive parts of growth hormone (GH), prolactin (PRL), adrenal cortical hormone (ACTH), thyroid-stimulating hormone (TSH), follicular stimulating hormone (FSH), and luteinizing hormone (LH)are mainly in the cytoplasm, Positive cells show yellow or brown particles. For each adenoma, a new section fixed in paraffin was taken to quantitatively evaluate the nuclear antigen Ki-67 positive (OriGene Technologies, Inc., antibody). Ki-67 positive cells showed yellow-brown particles. Five fields containing positive cells were randomly selected, and the total number of tumor cells and the total number of positive cells were calculated in the high-power field (400×) to calculate the percentage of positive cells. The above results were observed under an optical microscope, and were finally reviewed by two experienced pathologists, and the average was taken as the final result.

Neuroradiological evaluation: All patients underwent preoperative and postoperative magnetic resonance imaging (MRI) using 3.0T superconducting magnetic resonance imaging system, including T1-weighted and T2-weighted 2 mm sagittal and coronal scans. Tumor size is defined as the largest diameter measured on the coronal plane of the MRI-enhanced T1-weighted image. According to their maximum diameter, tumors are divided into macroadenomas (maximum diameter> 10 mm) and giant adenomas (maximum diameter> 40 mm).

Invasiveness: Invasive evaluation includes imaging and histology.i) Knosp classification III～IV in imaging evaluation (Knosp, 1993),ii) the histopathological evaluation confirmed invasiveness, iii) intraoperative neurosurgeon confirmed to invade surrounding tissues.

Recurrence: Patients with pituitary adenoma usually have routine MRI examinations 6 months after resection. Recurrence was defined as residual tumor progression or new tumor growth after tumor resection (Losa, 2008);i) previous surgical history of pituitary adenoma, ii) compared with the last postoperative examination, the imaging examination showed that the volume of new tumor or residual tumor increased, iii) laboratory examination showed that the average plasma hormone level decreased or returned to normal after the operation, then the hormone level rebounded, and iv) the clinical symptoms reappear or worsen after the operation.

Pituitary apoplexy: Pituitary adenoma that is hemorrhage or infarction expands rapidly in the sella, which in turn oppresses nearby structures (Mou, 2009);i) typical clinical evidence (sudden headache, dizziness, nausea, vomiting, and visual field changes),ii) neuroimaging shows evidence of hemorrhage,iii) intraoperative confirmation, andiv) pathological confirmation.

Hormone assessment: Patients were evaluated for ACTH, PRL, GH, TSH, FSH, LH serum hormone levels before surgery.the result was interpreted according to the normal range of our laboratory.

Statistical analysis: SPSS v21.0 statistical software (IBM Corp.Armonk, New York, USA) was used for data analysis.Continuous variables are expressed as mean ± standard deviation (x±s).According to the central limit theorem or the law of large numbers, for data with a sample size ≥ 30, the normality of the data can be used.The new pathological classification was used to compare the clinical and tumor characteristics of different tumor subtypes. The Student t test was used for continuous variables and statistical analysis ofthe association between Ki-67 indicators.For categorical variables (incidence rate, etc.), categorical variable chi-square test or Fisher's test was performed.$P<0.05$ was considered statistically significant.

RESULTS

Patient and tumor characteristics: From 2018 to 2019, a total of482 patients with surgically treated pituitary adenoma were registered in our case database, and 220 (45.6%) patients with SPA (55.9% female, mean age 55.25±11.12 years).The clinical symptoms are mainly related to the tumor mass effect. Among them, visual field impairment accounts for 59.5%, headache accounts for 37.7%, oculomotor palsy accounts for 4.1%, and accidental findings account for 19.5%.41.8% of patients observed a slight increase in serum prolactin levels (values between 13.32-191 μg/L), and 32.2% of patients observed a decrease in at least one pituitary hormone level.

In the preoperative imaging evaluation, patients with pituitary apoplexy accounted for 9.5%.The imaging Knosp grade III ~ IV and histological evaluation find totally of 102 patients (46.3%) with invasive evidence, the average maximum tumor diameter was 29.0 ± 9.8mm.The mean Ki-67 proliferation index of the tumor was 2.9±1.4%.The general clinical characteristics ofsilent adenoma are shown in Table 1, and the detailed information of each classification and subtype is shown in Fig 2 A-C.

Table 1. Clinical, endocrine and tumor characteristics of patients with silent pituitary adenoma

Age, $\bar{x}\pm s$(year)	55.25±11.1
Female, *n* (%)	123 (55.9)
Clinical symptoms	
Visual deficit, *n* (%)	131 (59.5)
Headache, *n* (%)	83 (37.7)
Incidentaloma, *n* (%)	43 (19.5)
Cranial nerve palsy, *n* (%)	9 (4.1)
Serum prolactin level, (ng/ml)	37.5±29.39
Hyperprolactinemia, *n* (%)	92 (41.8)
Hypopituitarism, *n* (%)	71 (32.2)
Tumor diameter, $\bar{x}\pm s$ (mm)	29.0±9.8
Invasive, *n* (%)	102 (46.3)
Apoplexy, *n* (%)	21 (9.5)
Recurrent, *n* (%)	34 (15.6)
Ki-67, $\bar{x}\pm s$ (%)	2.9±1.4

Table 2. The clinical, biochemical, and tumor characteristics of thesilent pituitary adenoma

	NCA(n=23)	SGAs (n=107)	SCA (n=74)	*P*
Age, $\bar{x}\pm s$(year)	57.5±8.06	56.7±10.07	54.2±10.5	0.116
Female, *n* (%)	7 (30.4)	40 (37.3)	68 (91.9)	0.001
Visual deficit, *n* (%)	10(43.4)	62(57.9)	51(68.9)	0.036
Hypopituitarism, *n* (%)	10 (43.5)	50 (46.7)	15 (20.3)	0.005
Tumor diameter, $\bar{x}\pm s$ (mm)	27±6.5	28±9.4	32±10	0.029
Giant adenoma, *n* (%)	1 (4.3)	10 (9.3)	13 (17.6)	0.060
Invasive, *n* (%)	12 (52.2)	44 (41.1)	39 (52.7)	0.131
Recurrent, *n* (%)	3 (13.0)	13 (12.1)	17 (22.9)	0.125
Apoplexy, *n* (%)	1 (4.3)	12 (11.2)	9 (12.2)	0.280
Ki-67, $\bar{x}\pm s$ (%)	3.59±2.1	2.89±0.13	2.58±0.99	0.006

Abbreviation. NCA, null cell adenoma; SCA, silent corticotroph adenoma; SGA, sparsely granulated somatotroph adenoma

Table 3. Classification of types of high-risk pituitary adenomasaccording to the new WHO classification

	Total	Male	Female
silent corticotroph adenoma	74	6	68
sparsely granulated somatotroph adenoma	4	1	3
PIT1-Positive Plurihormonal Adenomas	3	2	1
Total	81	9	72

Table 4.Comparison of invasiveness, recurrence, and apoplexy rates of high-risk and low-risk pituitary adenomas according to the new WHO classification

	High-risk	Low-risk	χ^2	*P*
Invasive, *n* (%)	43 (53.1)	58 (41.7)	3.264	0.035
Recurrent, *n* (%)	18 (22.0)	16 (11.5)	4.223	0.033
Apoplexy, *n* (%)	12 (14.8)	9 (6.5)	4.123	0.021

Table 5. Comparison of invasive pituitary adenoma and non-invasive pituitary adenoma Ki-67 according to the new WHO classification

	Invasive	Non-invasive	*t*	*P*
Gonadotropin adenomas	3.32±1.48	2.56±1.21	2.905	0.002
Corticotroph adenomas	2.77±1.10	2.39±0.85	1.650	0.050
Null cell adenoma	4.16±2.44	2.97±1.76	1.283	0.106
plurihormonal and double adenoma	1.70	2.88±1.41	-	-
Somatotroph adenoma	8.00	3.48±0.59	-	-
PIT1-Positive Plurihormonal Adenomas	3.33	-	-	-
Lactotroph adenoma	4.20	-	-	-
Thyrotroph adenoma	-	2.80	-	-
Total	3.26±1.64	2.59±1.18	3.415	0.001

Table 6. The invasion rate according to the recurrence in the silent pituitary adenoma

	Recurrent	Non-Recurrent	Statistics	*P*
Invasive	23	79	$\chi 2$=8.922	0.002
Ki-67	3.05±1.34	2.86±1.46	*t* =0.689	0.245

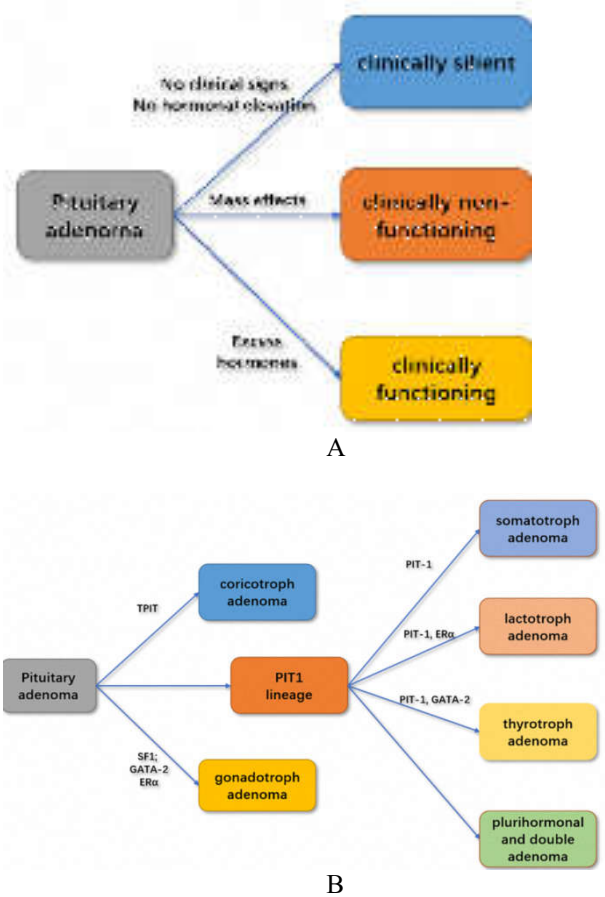
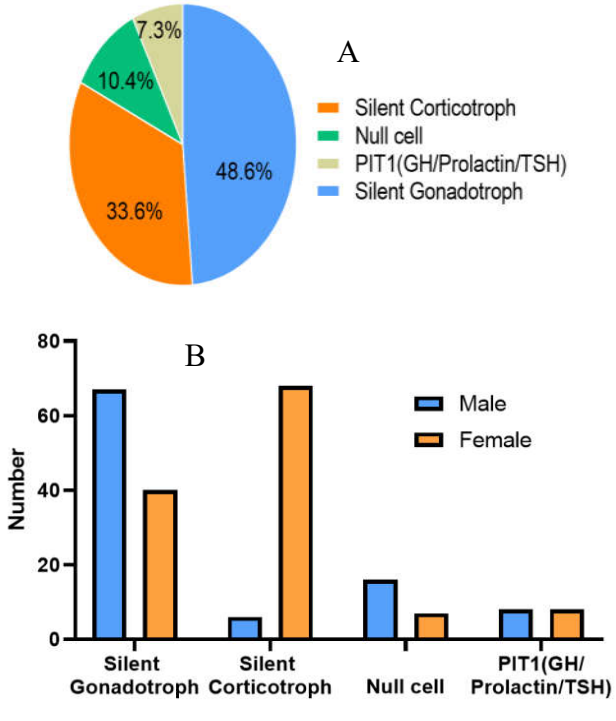


Figure 1.A) Clinical presentation classification, and B) Pathological transcription factors classification.



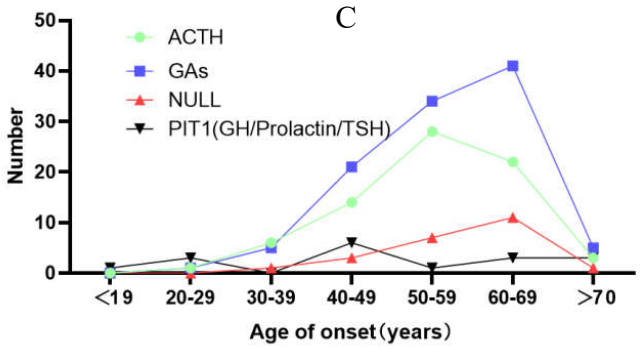


Figure 2.A) Pathological classification of silent pituitary adenoma, sparsely granulated somatotroph adenoma (SGA), silent corticotroph adenoma (SCA) and null cell adenoma(NCA) accounted for 92.72%; B) The gender distribution of silent pituitary adenoma subtypes, SCA has a significant female advantage 1:8.5 (*P*<0.0001), SGAs have a male advantage of 1.68:1 (*P*<0.001); C) The peak incidence of silent pituitary adenoma is between 40 and 70 years old. The proportion of patients in this age group is about 85.9% . The peak incidence of SCA is earlier than that of SGAs and NCA.

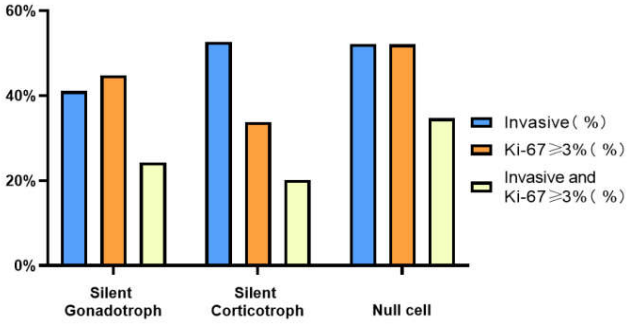


Figure 3.The null cell adenoma(NCA) is more invasive, and the Ki-67 index is higher.DGSA, densely granulated somatotroph adenoma; ERa, estrogen receptor a; GH, growth hormone; ACTH, Adreno corticotropic hormone; TSH, Thyroid stimulating hormone; PRL, prolactin; SCA, silent corticotroph adenoma; SF1, steroidogenic factor 1; SGA,silent gonadotroph adenoma; SGSA, sparsely granulated somatotroph adenoma; SPA,silent pituitary adenoma; NCA, Null cell adenoma; PIT-1, pituitary-specific POU-class homeodomain transcription factor; T-PIT, T-box family member TBX19; GATA2 , GATA transcription factor 2.

Characteristics comparisonaccording to the histopathological subtype: Table 2 and Fig 3 describe the clinical, biochemical, and tumor characteristics of these tumors.

Aggressive pituitary adenoma: The new version of the 2017 WHO Endocrine Organ Tumor Classification proposes 5 high-risk adenomas that may have aggressive characteristics. This study included three types of high-risk adenoma, including 74 cases of silent corticotroph adenoma, 4 cases of sparsely granulated somatotroph adenoma, and 3 cases of PIT1-Positive Plurihormonal Adenomas (Table 3).Pituitary adenomas in the high-risk group were higher than those in the low-risk group in terms of invasive, recurrence and apoplexy (*P*<0.05) (Table4).For the comparison between the invasive group and the non-invasive group, it was found that Ki-67 in the invasive group was significantly higher than that in the non-invasive group (*P*<0.001) (Table 5).The invasion rate was significantly higher in the recurrence group (*P*<0.05) (Table 6).

DISCUSSION

The new 2017 WHO Endocrine Organ Tumor Classification regards SPA as a special variant of its corresponding

functional adenoma, while one chapter is reserved only for null cell adenoma, that is, null cell adenoma is the only non-corresponding tumor of functional adenoma.Although SPA is not classified separately, this particular category of tumors often presents with macroadenomas and high invasive. In this study, the average diameter of the tumor was 29±9.8mm, and the proportion of giant adenomas was 11.81%, the proportion of macroadenomas was 88.19%.The invasive pituitary adenoma is 46.3%.Headache and visual impairment are more common in clinical symptoms, accounting for 37.7% and 59.5%, respectively. Although the symptoms of oppression of the optic nerve are more common and the proportion of patients with cavernous sinus invasion is higher, patients with oculomotor palsy are relatively rare, accounting for 4.1%, similar to other reports (Aflorei 2014; Daly, 2006; Ezzat, 2004; Lloyd, 2004).The incidence of pituitary stroke patients is 9.5%, which is similar to other references (Ezzat, 2004).

In the previous2004 WHO classification of pituitary adenomas, relevant studies have shown that null cell adenomas and PRL adenomas are most common (Jaffe, 2006; Molitch, 2008;Monson, 2000).Under the new 2017 WHO Endocrine Organ Tumor Classification redefines null cell adenoma, the original null cell adenoma can be further classified by transcription factor immunohistochemistry, which greatly reduces the number of tumors in this category of null cell adenoma.According to the research report by Nishioka H et al., the incidence of null cell adenoma in the old classification is 23% (Nishioka, 2015), while the incidence of null cell adenoma in the new version is reduced to 1%.In this study, silent gonadotroph adenoma, silent corticotroph adenoma, and null cell adenoma accounted for 92.7%, of which silent gonadotroph adenomas were the most common, and null cell adenoma accounted for about 10.5%.

In the previous 2004WHO classification, the clinical symptoms of null cell adenoma and gonadotroph adenoma are similar, and the pathological differences are not related to the clinical symptoms.In the absence of clear guidelines, it is difficult to distinguish between gonadotroph adenoma and null cell adenoma.However, by applying a new pathological definition, many tumors previously identified as null cell adenoma are likely to be actually hormone-negative pituitary adenoma, especially hormone-negative gonadotroph adenoma, which greatly affects our previous understanding of the clinical behaviours of null cell adenoma (Kontogeorgos, 2016).The difference between null cell adenoma and silent gonadotroph adenoma in the new classification has great clinical significance because null cell adenoma may be more aggressive than SPA (Almeida, 2019; Balogun, 2015).Silent corticotroph adenoma usually presents as a macroadenomas associated with tumor mass effects and is one of the five high-risk subtypes of adenoma (Cho, 2010; Lloyd, 2017).In our study, patients with silent corticotroph adenoma were younger, overall showed a female advantage, and the tumor diameter was larger, the proportion of giant adenoma was higher, and the proportion of patients with visual field impairment was higher, and the adenoma also has a higher invasive rate and a higher recurrence rate.Patients with silent gonadotroph adenoma showed male advantage, with a higher proportion of patients with hypopituitarism. Patients with null cell adenoma have a higher invasive rate and a higher Ki-67 index, and tumor proliferation is more active. Silent somatotroph adenoma is a GH immunoreactive tumor and lacks clinical and biological signs of acromegaly.

According to the new 2017 WHO classification of endocrine tumors, adenomas that secrete growth hormone can be subdivided into dense granules (DGSAs) and sparse granules (SGSA).Distinguishing between these two subtypes is of clinical significance because SGSA adenomas are usually more aggressive and may not respond well to somatostatin analogue therapy (Gomez-Hernandez, 2015).In a retrospective study (Chinezu, 2017), 21 silent and 59 somatotroph adenoma were compared, 85.7% of silent somatotroph adenoma were SGSA, and silent somatotroph adenoma may be more likely to be sparse granular, this study included 5 cases of silent somatotroph adenoma, of which 4 cases were sparsely granulated somatotroph adenoma.

The new classification removes the controversial diagnostic name "atypical pituitary adenoma" from the old version, and at the same time, proposes the concept of "aggressive pituitary adenoma", emphasizing the invasive growth of adenoma and its rapid growth, routine treatment resistance and or early/multiple relapses (Lloyd, 2004).At present, the new version of the classification for the concept of aggressive pituitary adenoma is mostly from the perspective of tumor characteristics and clinical outcomes, and there is a lack of reliable pathological tumor predictors and specific related diagnostic indicators. However, the new version of the classification proposes five types of high-risk subtype adenomas that may be aggressive. This study included three types of high-risk adenoma, including 74 cases of silent corticotroph adenoma, accounting for 91%, 4 cases of sparsely granulated somatotroph adenoma, and 3 cases of PIT1-Positive Plurihormonal Adenomas. The invasive rate of pituitary adenoma in the high-risk group was 53.1%, the recurrence rate was 22%, and the apoplexy rate was 14.8%. The invasive, recurrence and apoplexy rate of the pituitary adenoma in the high-risk group were higher than those in the low-risk group ($P<0.05$).For the comparison between the invasive group and the non-invasive group, it was found that Ki-67 in the invasive group was significantly higher than that in the non-invasive group ($P<0.001$), which is similar to other references (Liu, 2020). The new 2017 WHO classification recommends the provision of pathological tumor value-added index (Ki-67, mitotic count, P53) as an important feature of tumor prognosis (Lloyd, 2017).

Although the WHO does not include tumor invasion in the classification of pituitary adenomas, (pathologists often do not have relevant invasion data obtained from neuroimaging studies or surgeons' surgical impressions), the WHO classification emphasizes that invasion should be considered as an important prognostic feature.In 2013, Trouillas et al. proposed a new 5-level classification of tumor prognosis, with tumor invasion and proliferation as the classification criteria (Trouillas, 2013). In our study, the invasion rate of the relapse group was 67.6%, and the Ki-67 index was 3.05±1.34. The invasion rate and Ki-67 index of the relapse group were higher than those of the non-relapse group. This study has the following limitations; i) the postoperative follow-up time of the patient is too short, and the recurrence of the patient after the operation cannot be well observed, and ii) postoperative radiotherapy and drug treatment were not included in the analysis of factors affecting tumor recurrence. Therefore, the follow-up study of cases is still underway in order to further study and analyze the relevant factors affecting tumor prognosis under the new classification.

Conclusion

Briefly, compared with the previous 2004 WHO classification, the new 2017 WHO classification is accurate and reasonable, and no longer requires expensive and complicated tumor ultrastructure analysis. The cooperation of the multidisciplinary diagnosis and treatment team is conducive to the accurate diagnosis of silent pituitary adenoma, also helpful for the choice of subsequent treatment. At present, we still need to evaluate new treatment options and new prognostic markers under the new version of the classification in order to achieve accurate judgment of their prognosis, guide the choice of clinical treatment options, and improve the quality of patient's life.

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ETHICS APPROVAL

The study protocol was approved by the institutional review boards of Samsung Changwon Hospital (SCMC 2019-05-002). All studies were conducted according to the guidelines of the Declaration of Helsinki for biomedical research. Informed consent was waived due to study's retrospective nature and minimal hazard to the participants.

CONFLICT OF INTERESTS

The authors declare that they have no competing interests to report.

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