Risk of Recurrence in Pituitary Neuroendocrine Tumors: A Prospective Study Using a Five-Tiered Classification

Gérald Raverot,[1,2,3] Emmanuelle Dantony,[2,4,5] Julie Beauvy,[1,2] Alexandre Vasiljevic,[2,3,6] Sara Mikolasek,[1] Françoise Borson-Chazot,[1,2] Emmanuel Jouanneau,[2,3,7] Pascal Roy,[2,4,5] and Jacqueline Trouillas[2,6]

[1]Fédération d'Endocrinologie, Groupement Hospitalier Est, Hospices Civils de Lyon, Bron F-69677, France; [2]Faculté de Médecine Lyon Est, Université Lyon 1, Lyon F-69372, France; [3]INSERM U1052, CNRS UMR5286, Cancer Research Centre of Lyon, Lyon F-69372, France; [4]Service de Biostatistique, Hospices Civils de Lyon, Lyon F-69003, France; [5]CNRS, UMR 5558, Equipe Biostatistique Santé, Villeurbanne F-69622, France; [6]Centre de Pathologie et de Biologie Est, Groupement Hospitalier Est, Hospices Civils de Lyon, Bron F-69677, France; and [7]Service de Neurochirurgie, Groupement Hospitalier Est, Hospices Civils de Lyon, Bron F-69677, France

Background: Most pituitary neuroendocrine tumors (PitNETs) show benign behavior, but a substantial number are invasive, recur, or resist medical treatment. Based on a retrospective case-control study, we recently proposed a classification of PitNETs of prognostic relevance. This prospective study aims to test the value of this classification in an independent patient cohort.

Methods: All patients who underwent PitNET surgery from 2007 to 2012 in one single center were included. Using a grading system based on invasion on magnetic resonance imaging, immunocytochemical profile, Ki-67, mitotic index, and p53 positivity, tumors were classified. Progression-free survival of the graded tumors was calculated by the Kaplan-Meier method and compared using the log-rank test. A multivariate analysis, using a Cox regression model, was also performed.

Results: In total, 365 patients had grade 1a PitNETs (51.2%), followed by grade 2a (32.3%), 2b (8.8%), and 1b tumors (7.7%). Of 213 patients with a follow-up, 42% had recurrent (n = 52) or progressive disease (n = 37) at 3.5 years. Grade was a significant predictor of progression-free survival ($P < 0.001$). Multivariate analysis indicated grade ($P < 0.001$), age ($P = 0.035$), and tumor type ($P = 0.028$) as independent predictors of recurrence and/progression. This risk was 3.72-fold higher for a grade 2b tumor compared with grade 1a tumor.

Conclusions: Our data suggest that classification of PitNETs into five grades is of prognostic value to predict postoperative tumor behavior and identifies patients who have a high risk of early recurrence or progression. It therefore will allow clinicians to adapt their therapeutic strategies and stratify patients in future clinical trials. **(*J Clin Endocrinol Metab* 102: 3368–3374, 2017)**

Pituitary neuroendocrine tumors (PitNETs) (1) are the second most common primary brain tumors (15.5% of all types) (2). These tumors, clinically classified into functioning and nonfunctioning, are considered benign. However, 30% to 45% invade the cavernous or sphenoid sinus (3, 4), and at least 15% are regarded as clinically aggressive based on their resistance to conventional treatment or recurrence during follow-up (5, 6).

The World Health Organization 2004 classification proposed the term "atypical adenoma" for pituitary endocrine tumors showing "borderline or uncertain behaviour" (7) and define these tumors as having "atypical morphological features suggestive of aggressive behaviour such as invasion growth. Other features included elevated mitotic index and a Ki-67 labeling index greater than 3%, as well as extensive nuclear p53

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 30 March 2017. Accepted 16 June 2017.
First Published Online 23 June 2017

Abbreviations: CI, confidence interval; HR, hazard ratio; MRI, magnetic resonance imaging; PitNET, pituitary neuroendocrine tumor.

immunostaining." Because of these vaguely defined criteria, the reported incidence of atypical adenoma varies widely, ranging from 2.9% (8) to 18.7% (9). Moreover, the few small studies that examined the prognostic usefulness of this classification delivered controversial results (4, 8–12).

To improve the prognostic assessment of PitNET series, we recently proposed a classification that stratifies resected PiNET patients into five grades, which consider the combination of invasion, proliferative markers (mitosis, Ki-67), and p53 expression. Grade 1a is defined as noninvasive, grade 1b as noninvasive but proliferative, grade 2a as invasive, grade 2b as invasive and proliferative, and grade 3 as metastatic. In this large case-control study that included all pituitary tumor subtypes, we demonstrated that grade 2b tumors had a poor prognosis with a 12-fold increased probability of tumor progression compared with grade 1a tumors (13). This risk classification was a major step forward toward a more personalized treatment of PitNETs (6, 14, 15), but as it was based on a retrospective study, its prognostic value needs to be confirmed in a prospective independent cohort. This was the aim of the current study.

Materials and Methods

Patients

Patients with a diagnosis of PitNET were identified from the pathological register of the Hospices Civils de Lyon, France (Centre de Pathologie et de Biologie Est, Groupement Hospitalier Est, Lyon). Among these, all patients having been operated on for the first time (*i.e.*, not recurrence) by a single expert neurosurgeon (E.J.) in the regional referral center of Lyon (Hospices Civils de Lyon) from February 2007 to October 2012 were included. Patient information, including sex, age at surgery, preoperative and postoperative hormonal data, postoperative treatments, and relevant medical events, was recorded in a local database (PITUICARE-Lyon, registered with the French data protection agency CNIL, 16-021, and clinicaltrials.org, NCT02854228). All patients underwent magnetic resonance imaging (MRI) at the time of diagnosis and prior to surgery to determine the tumor size and to classify them as microadenomas (diameter <1 cm), macroadenomas (1 to 4 cm), or giant adenomas (>4 cm). Tumor invasion was evaluated on the preoperative MRI for all patients. Invasion of the cavernous sinus but not the suprasellar expansion was considered. Sphenoid sinus invasion was taken into account only if it was peroperatively confirmed by the surgeon and/or by histology. Hormonal levels were measured before surgery, 1 to 3 months and 1 year after surgery, and then yearly. Postoperative MRI was performed 3 months postsurgery and then every 6 to 12 months according to the presence of residual tumor.

Pituitary tumors

For each tumor, fragments were fixed in zinc-formalin and embedded in paraffin for pathological diagnosis. The immunoprofile was determined by automated immunostaining using antibodies against adrenocorticotropic hormone, growth hormone, prolactin, β–follicle-stimulating hormone, β–luteinizing hormone, and β–thyroid-stimulating hormone (13). The plurihormonal tumors were classified according to the prevailing hormone expression. The proliferative activity of each tumor was assessed on the basis of number of counted mitoses and the Ki-67 index (13). In addition, p53 nuclear staining was analyzed. Cells from 10 representative high-power fields of 0.30 mm^2 (×400 magnification) per tumor were counted with an average count of 5000 nuclei. Ki-67 labeling was expressed as a maximum percentage and mitoses by their absolute number. The detection of p53 was considered positive if >10 strongly positive nuclei per 10 high-power fields were recorded (13).

Classification of the tumors

All tumors were classified based on a combination of criteria: MRI features (tumor size and invasion) and immunocytological characteristics (immunosubtype, Ki-67 index, mitotic count, and p53 positivity) (13). This led to the stratification of the tumors into five grades: grade 1a, noninvasive; grade 1b, noninvasive and proliferative; grade 2a, invasive; grade 2b, invasive and proliferative; and grade 3, metastatic (Table 1). All tumors were assessed and classified independently by two pathologists (J.T. and A.V.).

Definition of progression-free survival

Patients in complete remission showing no evidence of disease during follow-up (no clinical symptoms, normal plasma hormone levels, and no visible radiological tumor remnant) were considered controlled. Patients with postoperatively active disease (increased plasma hormone levels with or without radiological evidence of a tumor) but controlled by medical treatment during follow-up were considered controlled. For progression-free survival analysis, patient follow-up started 1 year after surgery. Patients were followed until tumor recurrence or progression or, for right-censored patients, until their last visit. Recurrence was defined as an increase in plasma hormone levels with or without radiological evidence of a tumor mass after previous remission in secreting PitNETs and appearance of tumor mass in gonadotroph PitNETs. Tumor progression was defined as evidence of regrowth of residual tumor on MRI and/or an increase in plasma hormone levels.

Statistical analysis

For the different grades, invasion, and the immunocytochemical profile, progression-free survival was estimated using

Table 1. Definition of Tumor Grade

	Invasion	
Proliferation	**No**	**Yes**
No	1a	2a
Yes	1b	2b

Invasion is defined as radiological (MRI) signs of cavernous or sphenoid sinus invasion. Proliferation is considered based on the presence of at least two of the following three criteria: mitoses, n > 2 per 10 high-power fields; Ki-67, ≥3%; p53, positive (>10 strongly positive nuclei per 10 high-power fields).

the Kaplan-Meier method. The progression-free survival curves obtained for grades were compared using the log-rank test; patients with missing data for the grade and thyrotroph tumors were excluded from this analysis. Multivariate progression-free survival analysis was performed using a Cox regression model. Factors considered *a priori* were tumor size (microadenoma *vs* macroadenoma and giant adenoma), immunosubtype, age, sex, invasion, and proliferation. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each parameter. Patients with missing data for the previously described factors and patients with thyrotroph tumors were excluded from analyses. A multiplicative model without interaction terms between the type and the grade components (invasion and proliferation) was fitted. A non-multiplicative joint effect of invasion and proliferation was tested by introducing an interaction term between these two components of the grade. Nested models were compared using the log-rank test. In all statistical tests (two-tailed), P values $<5\%$ were considered significant, except for interaction tests for which a threshold of 10% was retained. All analyses were performed using R software (http://www.R-project.org/).

Results

Patient and tumor characteristics

The flowchart of the study is presented in Fig. 1. Among the 405 patients identified, 31 were excluded: 3 for lack of available pathological classification due to tumor apoplexia and 28 for second surgery of recurrent tumors (the first surgery had occurred before the study period). The study population included 374 patients (194 women and 180 men), and the mean ± standard deviation age at surgery was 51.9 ± 15.8 years. From MRI classification, 82.1% were macroadenomas, 4.3% giant adenomas, and 13.6% microadenomas. Invasion of the cavernous sinus and/or sphenoid sinus was evident for 41.1% of cases. Patients most frequently had gonadotroph tumors (n = 185, 49.5%), followed by somatotroph (n = 90, 24.0%), corticotroph (n = 52, 13.9%), and lactotroph (n = 43, 11.5%; Table 2) tumors.

Among the 365 tumors for which grade was available (grade was not evaluable for nine tumors due to missing data regarding invasion or pathological markers), grade 1a tumors were the most frequent (51.2%), followed by grades 2a (32.3%), 2b (8.8%), and 1b (7.7%). Of the 60 proliferative tumors (grades 1b and 2b), 48 of 60 (80.0%) had two proliferative markers, and 12 of 60 (20%) had three proliferative markers. For tumors with only two proliferative markers, Ki-67 >3% (45/48 cases; 93.8%) was associated with p53 positivity in 38 tumors and elevated mitosis number in 7 tumors. Association of p53 positivity and elevated mitosis number was presented in only three tumors (Supplemental Table 1).

For grade 1a and 2a tumors (n = 305), only one marker was present in 66 tumors (Ki-67 ≥3%: n = 29, 9.5%; mitotic count >2: n = 9, 3.0%; p53: n = 28, 9.2%). A total of 239 tumors did not present any proliferative marker (information for one marker was missing for 17).

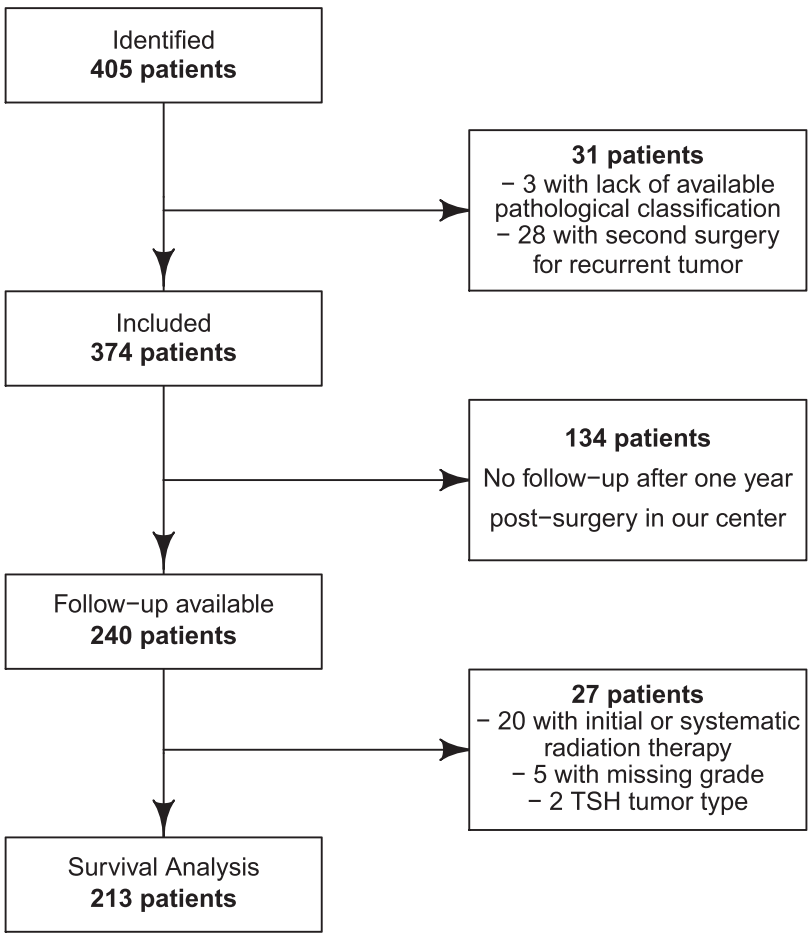

Figure 1. Study flowchart. TSH, thyroid-stimulating hormone.

Progression-free survival

From the initial cohort, 240 patients were followed in our center (134 patients were followed by other centers). Among these, 20 underwent adjuvant radiation therapy during the first postoperative year, including 5 corticotroph tumors, 10 gonadotroph tumors, 4 somatotroph tumors, and 1 thyrotroph tumor. These tumors were invasive macroadenomas (n = 15) or giant tumors (n = 5) that were classified as grade 2a (n = 11) or 2b (n = 9), and all were excluded from the progression-free survival analysis. The mean ± standard deviation length of follow-up was 3.5 ± 1.9 years. Among the 213

Table 2. Clinical and Tumor Characteristics

Characteristic	Total (N = 374)	Follow-Up Cohort (n = 240)	Absence of Follow-Up[a] (n = 134)
Age (y), mean ± SD	51.9 ± 15.8	50.2 ± 16.0	55.0 ± 14.9
Length of follow-up (years), mean ± SD	2.5 ± 2.1	3.5 ± 1.9	0.33 ± 0.17
Number of missing data	19	0	19
Sex, n (%)			
Male	180 (48.1)	114 (47.5)	66 (49.3)
Female	194 (51.9)	126 (52.5)	68 (50.7)
Tumor size, n (%)			
Microadenoma	51 (13.6)	33 (13.7)	18 (13.4)
Macroadenoma	307 (82.1)	197 (82.1)	110 (82.1)
Giant adenoma	16 (4.3)	10 (4.2)	6 (4.5)
Tumor type, n (%)			
Lactotroph	43 (11.5)	27 (11.3)	16 (11.9)
Gonadotroph	185 (49.5)	114 (47.5)	71 (53.0)
Corticotroph	52 (13.9)	34 (14.2)	18 (13.4)
Somatotroph	90 (24.0)	63 (26.2)	27 (20.2)
Thyrotroph	4 (1.1)	2 (0.8)	2 (1.5)
Classification, n (%)[b]			
1a	187 (51.2)	109 (46.4)	78 (60.0)
1b	28 (7.7)	18 (7.6)	10 (7.7)
2a	118 (32.3)	82 (34.9)	36 (27.7)
2b	32 (8.8)	26 (11.1)	6 (4.6)

Abbreviation: SD, standard deviation.

[a]Follow-up <1 year.

[b]Missing for nine patients.

patients analyzed (Fig. 1), 89 experienced an event during follow-up (41.8%); this was a recurrence for 52 and a progression for 37.

The Kaplan-Meier progression-free survival curves obtained for different grades [Fig. 2(a)], invasion [Fig. 2(b)], and the immunocytochemical profile [Fig. 2(c)] were statistically different (log-rank test, $P < 0.001$ for grade and invasion, and $P = 0.007$ for immunocytochemical profile). For the grade, the differences were mainly due to the effect of invasion (comparison of curves of grades 1a and 2a), with the effect of proliferation (grades 1a *vs* 1b) being lower than the one of invasion [Fig. 2(a)].

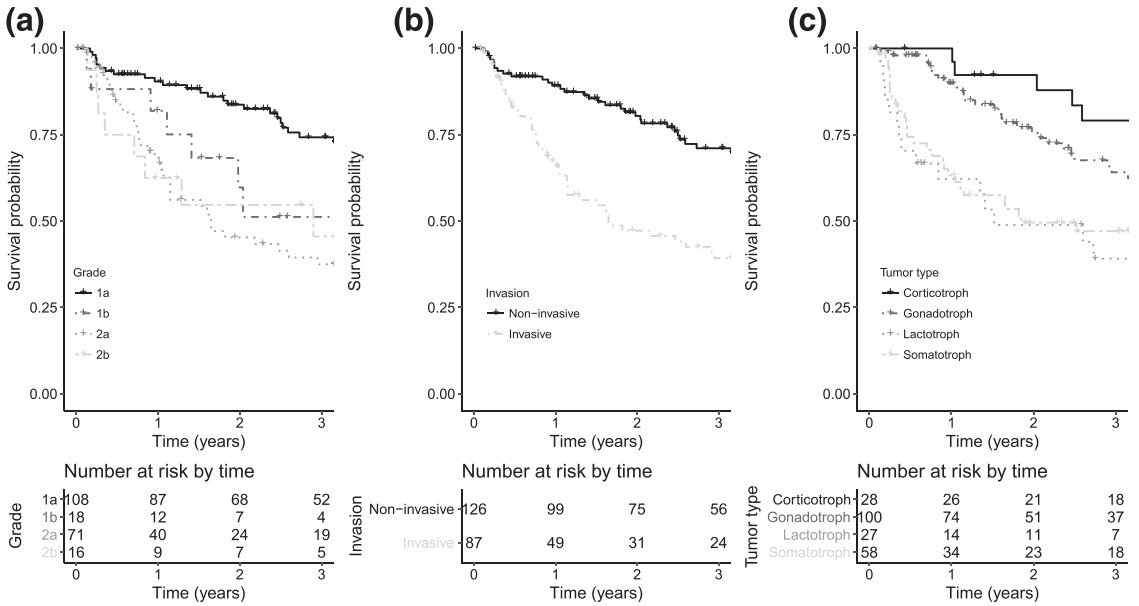

Figure 2. Kaplan-Meier progression-free survival analysis according to (a) the different tumor grades, (b) invasion, and (c) the immunocytochemical profile. There was a significant difference between progression-free survival curves: log-rank tests were $P < 0.001$ for grade and invasion and $P = 0.007$ for immunocytochemical profile. On the x-axis, time 0 years corresponds to 1 year postsurgery. Crosses on the progression-free survival curves represent censored patients.

Results of the multivariate Cox analysis are presented in Table 3. Age ($P = 0.035$), tumor type ($P = 0.028$), and grade ($P < 0.001$) were significantly associated with the risk of recurrence/progression, whereas sex and initial tumor size were not. No interaction between the two grade components (invasion and proliferation) was found ($P = 0.119$). Irrespective of tumor type, grade 2b was associated with the risk of recurrence/progression with respect to grade 1a tumors (HR, 3.72; 95% CI, 1.90 to 7.26). Among the grading components, invasion was significantly associated with recurrence for grade 2a (HR, 2.98; 95% CI, 1.89 to 4.70), whereas proliferation was not significantly associated with prognosis for grade 1b (HR, 1.25; 95% CI, 0.73 to 2.13).

Discussion

This prospective study validates the prognostic value of our proposed clinicopathological classification in a large cohort with a long postoperative follow-up. Tumor grade proved to be a significant predictor of recurrence and/or progression. Grade 2b tumors, representing ~10% of all surgically treated pituitary tumors, had a 3.7-fold increased risk of recurrence or progression compared with grade 1a tumors.

The classification relies on two basic criteria: invasion assessed by MRI and proliferation, determined by morphology. Invasion of surrounding structures, such as the sphenoid or cavernous sinus, was strongly associated with poor postoperative prognosis. Whether extension of the tumor is a consequence of its biological properties or due to the fact that the medial wall of the cavernous sinus is extremely thin is still a matter of debate (16). The association of many markers with invasion and aggressiveness suggests that the biological properties of the tumor may determine invasion (17–19). Furthermore, invasion is recognized as being the major criterion for surgical failure to remove the entire tumor (20), yet persistence of postoperative residual tumors has been reported not to predict the risk of progression or resistance to medical treatment (for lactotroph or somatotroph tumors) (21–23). This indicates that additional risk factors have to be considered. The use of morphological markers for determining the prognosis of PitNETs has produced controversial data. The reason for this is probably that various cutoffs for the Ki-67 index, ranging from 1.3% (7, 24) to 10% (14) and sometimes adapted to tumor subtype (25), were applied to identify tumors with high risk of recurrence. Furthermore, most studies were based on a limited number of cases, an expert opinion (14), and retrospective analysis. Ki-67 index alone has been regarded as insufficient to predict tumor behavior. The prognostic value of the immunopositivity for p53, a criterion of the World Health Organization classification, has also been debated because a reliable method of quantification was missing (6). Recent studies, however, defined p53 staining as positive if >10 nuclei per 10 high-power fields were strongly labeled (8, 13, 24, 26). In the current study, we demonstrate that a Ki-67 index >3% has a major impact on PitNET prognosis. First, this Ki-67 value was found in the majority of proliferative grade 1b and 2b tumors and only rarely in nonproliferative grade 1a and 2a tumors. Second, p53 positivity was much more frequent in tumors with Ki-67 ≥3% (83.3%) than in those with a Ki-67 <3% (11.7%; Supplemental Table 2). The frequency of grade 2b tumors in our series is within

Table 3. Factors Associated With Recurrence/Progression-Free Survival

Characteristic	Patients (n = 213)	HR (95% CI)	*P* Value[a]
Age (y), mean ± SD	50.4 ± 16.3	0.98 (0.97–1.00)	0.035
Sex, n (%)			0.312
Male	97 (45.5)	1.00	
Female	116 (54.5)	0.79 (0.50–1.25)	
Tumor size, n (%)			0.419
Microadenoma	33 (15.5)	1.00	
Macroadenoma/giant adenoma	180 (84.5)	1.34 (0.65–2.76)	
Tumor type, n (%)			0.028
Lactotroph	27 (12.7)	1.00	
Gonadotroph	100 (47.0)	0.57 (0.28–1.15)	
Corticotroph	28 (13.1)	0.45 (0.19–1.08)	
Somatotroph	58 (27.2)	1.07 (0.56–2.06)	
Classification, n (%)			<0.001
1a	108 (50.7)	1.00	
1b	18 (8.5)	1.25 (0.73–2.13)	
2a	71 (33.3)	2.98 (1.89–4.70)	
2b	16 (7.5)	3.72 (1.90–7.26)	

Abbreviation: SD, standard deviation.

[a] *P* values were calculated from likelihood ratio tests.

the range reported for "atypical adenoma" (2.9% to 18.7%), as defined by the World Health Organization classification (4, 9, 11, 12). Tumors operated upon for recurrence (which are included in most other studies) were excluded from the current study (n = 28), although many were grade 2b tumors (n = 11). This also underlines that the group of recurrent PitNETs needing second surgery contains many grade 2b tumors.

The mean follow-up of 3.5 years might be considered short since pituitary tumors can take many years before recurrence or regrowth. However, despite this apparent short follow-up period, we were able to identify a group of tumors with higher risk of recurrence/progression that could be considered the more aggressive tumors. Longer follow-up would allow the identification of tumors with late recurrence that could occur for each subgroup, yet the results do allow the identification of more aggressive tumors that may benefit from an intensive therapeutic strategy (*i.e.*, radiation therapy) or closer follow-up.

Despite the high remission rate 1 year after the operation (172/213, 80.6%; Supplemental Table 3) in our cohort, the incidence of recurrence/progression (despite medical treatment) was elevated during follow-up. Initial remission did not predict long-term prognosis. Similar results have been published by Tampourlou *et al.* (27) in a retrospective study of a cohort of clinically nonfunctioning PitNETs with a recurrence rate of 31% and, more important, a second regrowth rate of 35.3% at 5 years with a lower risk of recurrence in case of radiotherapy. The authors did not find predictive factors of recurrence, but pathological data were not analyzed. This study underlined that a standardized prognosis classification is needed to allow an early identification of patients with a high risk of recurrence and aid decision making for all clinicians involved in the management of these patients. The risk classification used herein may be further refined by additional studies considering tumors that are rarer than those included herein. Some authors believe that only certain morphological subtypes are prone to aggressive behavior (such as Crooke cell tumor, silent corticotroph tumor, silent subtype 3 tumors) (6, 28). This assumption is based on the high incidence of silent corticotroph tumors among the pituitary carcinomas, most of them published as case reports. Silent corticotroph tumors represent <10% of all corticotroph tumors (29), silent somatotroph tumors represent 2% of surgical series (30), and other subtypes are even rarer. Focusing attention on some rare subgroups of PitNETs will not help clinicians treat the majority of these tumors.

In conclusion, this prospective study confirms the usefulness of our previously proposed classification and may now allow clinicians to adapt their therapeutic strategies according to prognosis, and it may also be used to stratify patients and evaluate therapeutic efficacy in future clinical trials. Further progress can be expected, particularly if an improved understanding of molecular abnormalities associated with pituitary tumorigenesis generates better biomarkers.

Acknowledgments

We thank Günter Klöppel for helpful discussions and review of the manuscript and Philip Robinson (Hospices Civils de Lyon) for help in manuscript preparation.

Address all correspondence and requests for reprints to: Gérald Raverot, MD, Fédération d'Endocrinologie du Pôle Est, Groupement Hospitalier Est, 59 Bd Pinel, F-69677 Bron, France. E-mail: gerald.raverot@chu-lyon.fr.

This work was supported by Ministère de la Santé Programme Hospitalier de Recherche Clinique National Grant 27-43 Hypophyse Pronostique (HYPOPRONOS) and Programme Hospitalier de Recherche Clinique National Institut National du Cancer (INCA) Grant 12-096 Pituitary Tumor Identification of Genetic markers (PITUIGENE).

Author contributions: G.R. conceived and planned the study and wrote the manuscript with input from all coauthors; E.D. and P.R. did statistical analyses and produced the tables and figures; A.V. and J.T. performed the pathological diagnosis and classified the tumors independently; J.B., E.J., F.B.-C., S.M., and G.R. contributed to patient information and verified all clinical and treatment details. All the authors revised the manuscript.

Clinical trial registry: ClinicalTrials.gov no. NCT02854228 (registered 17 July 2013) PITUICARE-Lyon.

Disclosure Summary: The authors have nothing to disclose.

References

1. Asa SL, Casar-Borota O, Chanson P, Delgrange E, Earls P, Ezzat S, Grossman A, Ikeda H, Inoshita N, Karavitaki N, Korbonits M, Laws ER Jr, Lopes MB, Maartens N, McCutcheon IE, Mete O, Nishioka H, Raverot G, Roncaroli F, Saeger W, Syro LV, Vasiljevic A, Villa C, Wierinckx A, Trouillas J; attendees of 14th Meeting of the International Pituitary Pathology Club, Annecy, France, November 2016. From pituitary adenoma to pituitary neuroendocrine tumor (PitNET): an International Pituitary Pathology Club proposal. *Endocr Relat Cancer*. 2017;**24**(4):C5–C8.
2. Ostrom QT, Gittleman H, Fulop J, Liu M, Blanda R, Kromer C, Wolinsky Y, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2008-2012. *Neuro Oncol*. 2015;**17**(Suppl 4): iv1–iv62.
3. Meij BP, Lopes MB, Ellegala DB, Alden TD, Laws ER Jr. The long-term significance of microscopic dural invasion in 354 patients with pituitary adenomas treated with transsphenoidal surgery. *J Neurosurg*. 2002;**96**(2):195–208.
4. Zada G, Woodmansee WW, Ramkissoon S, Amadio J, Nose V, Laws ER Jr. Atypical pituitary adenomas: incidence, clinical characteristics, and implications. *J Neurosurg*. 2011;**114**(2): 336–344.
5. Raverot G, Castinetti F, Jouanneau E, Morange I, Figarella-Branger D, Dufour H, Trouillas J, Brue T. Pituitary carcinomas and aggressive pituitary tumours: merits and pitfalls of temozolomide treatment. *Clin Endocrinol (Oxf)*. 2012;**76**(6):769–775.

6. Di Ieva A, Rotondo F, Syro LV, Cusimano MD, Kovacs K. Aggressive pituitary adenomas—diagnosis and emerging treatments. *Nat Rev Endocrinol*. 2014;**10**(7):423–435.
7. Lloyd RV, Kovacs K, Young WF Jr, Farrel WE, Asa SL, Trouillas J, Kontogeorgos G, Sano T, Scheithauer BW, Horvath E, Watson RE Jr, Lindell EP, Barkan AL, Saeger W, Nosé V, Osamura RY, Ezzat S, Yamada S, Roncaroli F, Lopes MBS, Vidal Ruibal S. Tumours of the pituitary. In: DeLellis RA, Lloyd RV, Heitz PU, eds. *Pathology and Genetics. Tumours of Endocrine Tumours*. Lyon, France: International Agency for Research and Cancer (IARC); **2004**:9–48.
8. Miermeister CP, Petersenn S, Buchfelder M, Fahlbusch R, Lüdecke DK, Hölsken A, Bergmann M, Knappe HU, Hans VH, Flitsch J, Saeger W, Buslei R. Histological criteria for atypical pituitary adenomas—data from the German pituitary adenoma registry suggests modifications. *Acta Neuropathol Commun*. 2015;**3**:50.
9. Chiloiro S, Doglietto F, Trapasso B, Iacovazzo D, Giampietro A, Di Nardo F, de Waure C, Lauriola L, Mangiola A, Anile C, Maira G, De Marinis L, Bianchi A. Typical and atypical pituitary adenomas: a single-center analysis of outcome and prognosis. *Neuroendocrinology*. 2015;**101**(2):143–150.
10. Saeger W, Lüdecke DK, Buchfelder M, Fahlbusch R, Quabbe HJ, Petersenn S. Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. *Eur J Endocrinol*. 2007;**156**(2):203–216.
11. Yildirim AE, Divanlioglu D, Nacar OA, Dursun E, Sahinoglu M, Unal T, Belen AD. Incidence, hormonal distribution and postoperative follow up of atypical pituitary adenomas. *Turk Neurosurg*. 2013;**23**(2):226–231.
12. Del Basso De Caro M, Solari D, Pagliuca F, Villa A, Guadagno E, Cavallo LM, Colao A, Pettinato G, Cappabianca P. Atypical pituitary adenomas: clinical characteristics and role of ki-67 and p53 in prognostic and therapeutic evaluation. A series of 50 patients. *Neurosurg Rev*. 2017;**40**(1):105–114.
13. Trouillas J, Roy P, Sturm N, Dantony E, Cortet-Rudelli C, Viennet G, Bonneville JF, Assaker R, Auger C, Brue T, Cornelius A, Dufour H, Jouanneau E, François P, Galland F, Mougel F, Chapuis F, Villeneuve L, Maurage CA, Figarella-Branger D, Raverot G, Barlier A, Bernier M, Bonnet F, Borson-Chazot F, Brassier G, Caulet-Maugendre S, Chabre O, Chanson P, Cottier JF, Delemer B, Delgrange E, Di Tommaso L, Eimer S, Gaillard S, Jan M, Girard JJ, Lapras V, Loiseau H, Passagia JG, Patey M, Penfornis A, Poirier JY, Perrin G, Tabarin A; members of HYPOPRONOS. A new prognostic clinicopathological classification of pituitary adenomas: a multicentric case-control study of 410 patients with 8 years postoperative follow-up. *Acta Neuropathol*. 2013;**126**(1):123–135.
14. Kovacs K, Rotondo F, Horvath E, Syro LV, Di Ieva A, Cusimano MD, Munoz DG. Letter to the editor. *Endocr Pathol*. 2014;**26**(1):93–94.
15. Raverot G, Vasiljevic A, Jouanneau E, Trouillas J. A prognostic clinicopathologic classification of pituitary endocrine tumors. *Endocrinol Metab Clin North Am*. 2015;**44**(1):11–18.
16. Saeger W, Petersenn S, Schöfl C, Knappe UJ, Theodoropoulou M, Buslei R, Honegger J. Emerging histopathological and genetic parameters of pituitary adenomas: clinical impact and recommendation for future WHO classification. *Endocr Pathol*. 2016;**27**(2):115–122.
17. Raverot G, Wierinckx A, Dantony E, Auger C, Chapas G, Villeneuve L, Brue T, Figarella-Branger D, Roy P, Jouanneau E, Jan M, Lachuer J, Trouillas J; HYPOPRONOS. Prognostic factors in prolactin pituitary tumors: clinical, histological, and molecular data from a series of 94 patients with a long postoperative follow-up. *J Clin Endocrinol Metab*. 2010;**95**(4):1708–1716.
18. Gürlek A, Karavitaki N, Ansorge O, Wass JAH. What are the markers of aggressiveness in prolactinomas? Changes in cell biology, extracellular matrix components, angiogenesis and genetics. *Eur J Endocrinol*. 2007;**156**(2):143–153.
19. Mete O, Hayhurst C, Alahmadi H, Monsalves E, Gucer H, Gentili F, Ezzat S, Asa SL, Zadeh G. The role of mediators of cell invasiveness, motility, and migration in the pathogenesis of silent corticotroph adenomas. *Endocr Pathol*. 2013;**24**(4):191–198.
20. Cortet-Rudelli C, Bonneville JF, Borson-Chazot F, Clavier L, Coche Dequéant B, Desailloud R, Maiter D, Rohmer V, Sadoul JL, Sonnet E, Toussaint P, Chanson P. Post-surgical management of non-functioning pituitary adenoma. *Ann Endocrinol (Paris)*. 2015;**76**(3):228–238.
21. Colao A, Grasso LF, Pivonello R, Lombardi G. Therapy of aggressive pituitary tumors. *Expert Opin Pharmacother*. 2011;**12**(10):1561–1570.
22. Colao A, Auriemma RS, Lombardi G, Pivonello R. Resistance to somatostatin analogs in acromegaly. *Endocr Rev*. 2011;**32**(2):247–271.
23. Gillam MP, Molitch ME, Lombardi G, Colao A. Advances in the treatment of prolactinomas. *Endocr Rev*. 2006;**27**(5):485–534.
24. Gejman R, Swearingen B, Hedley-Whyte ET. Role of Ki-67 proliferation index and p53 expression in predicting progression of pituitary adenomas. *Hum Pathol*. 2008;**39**(5):758–766.
25. Righi A, Agati P, Sisto A, Frank G, Faustini-Fustini M, Agati R, Mazzatenta D, Farnedi A, Menetti F, Marucci G, Foschini MP. A classification tree approach for pituitary adenomas. *Hum Pathol*. 2012;**43**(10):1627–1637.
26. Thapar K, Scheithauer BW, Kovacs K, Pernicone PJ, Laws ER Jr. p53 expression in pituitary adenomas and carcinomas: correlation with invasiveness and tumor growth fractions. *Neurosurgery*. 1996;**38**(4):765–771, discussion 770–771.
27. Tampourlou M, Ntali G, Ahmed S, Arlt W, Ayuk J, Byrne JV, Chavda S, Cudlip S, Gittoes N, Grossman A, Mitchell R, O'Reilly MW, Paluzzi A, Toogood A, Wass JAH, Karavitaki N. Outcome of non-functioning pituitary adenomas that regrow after primary treatment: a study from two large UK centers. *J Clin Endocrinol Metab*. 2017;**102**(6):1889–1897.
28. Sav A, Rotondo F, Syro LV, Di Ieva A, Cusimano MD, Kovacs K. Invasive, atypical and aggressive pituitary adenomas and carcinomas. *Endocrinol Metab Clin North Am*. 2015;**44**(1):99–104.
29. Raverot G, Wierinckx A, Jouanneau E, Auger C, Borson-Chazot F, Lachuer J, Pugeat M, Trouillas J. Clinical, hormonal and molecular characterization of pituitary ACTH adenomas without (silent corticotroph adenomas) and with Cushing's disease. *Eur J Endocrinol*. 2010;**163**(1):35–43.
30. Chinezu L, Vasiljevic A, Trouillas J, Lapoirie M, Jouanneau E, Raverot G. Silent somatotroph tumour revisited from a study of 80 patients with and without acromegaly and a review of the literature. *Eur J Endocrinol*. 2016;**176**(2):195–201.