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MINI REVIEW

Non-functioning pituitary adenomas: growth and aggressiveness

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Abstract Pituitary adenomas (PAs) are common, comprising approximately one third of all intracranial tumors. Non-functioning pituitary adenomas (NFPAs) are the most common PAs. Although usually benign, the NFPAs represent therapeutic challenges because of their location close to the optic chiasm and nerves, and the proximity to the pituitary gland. The therapeutic alternatives are surgery and radiation. To date there is no effective medical treatment. NFPAs are classified according to different modalities, but there are no reliable marker of aggressiveness to guide the clinician in monitoring the patient. More information on growth patterns with constituent biological markers are needed to tailor the care of this patient group. Studies characterizing the membrane receptors of NFPAs have shown promising results, which may give rise to the development of medical treatment.

Keywords Non-functioning pituitary adenomas · Pituitary adenomas · Silent pituitary adenomas · Growth kinetics · Prognosis · Aggressiveness

Introduction

Pituitary adenomas (PAs) are common, comprising approximately one third of all intracranial tumors [1]. With the increasing access to cerebral imaging, pituitary tumors are increasingly identified by chance, when an investigation is performed for another reason than a suspicion of a pituitary disease—the definition of a pituitary incidentaloma.

Although usually benign, the Non-functioning pituitary adenomas (NFPAs) represent therapeutic challenges because of their location close to the optic chiasm and nerves, and the proximity to the pituitary gland. NFPAs clinically manifest late in the development, at the time when they cause mass effect on surrounding tissue (visual impairment, headache) or affect pituitary hormonal secretion. Visual field abnormality is the presenting symptoms in 87 % of the patients and headaches in 66 % [2]. This is contrary to hormone-secreting PAs normally detected at an earlier stage because of characteristic signs and symptoms [3]. Approximately, half of the patients with NFPA have pituitary deficiency in at least one of the pituitary axes [2, 4]. An example of a patient course is given in Textbox 1 with constituting illustrations of MR-investigations and growth curve in Fig. 1.

The PAs are in most cases sporadic, however up to 5 % are familial adenomas, either as part of the multiple endocrine neoplasia syndrome (MEN1) or familial isolated pituitary adenomas (FIPAs), often caused by mutations in the *AIP*-gene [5]. Also, an increasing number of incidentalomas are found on MRI or computed tomography (CT), raising questions on how to be handled [6].

The study and treatment of NFPAs are challenging not only due to the location at the skull base and because of the complex functions of the pituitary gland, but also due to the restricted tissue availability and the lack of animal models adequately mimicking human pituitary tumorigenesis.

Epidemiology

The exact prevalence of PAs is difficult to estimate, because of the variation in clinical presentation and the study methods or the registers used. A recent nationwide,

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Textbox 1 NFPA patient course

Female, 36-year old. Elevated prolactin, 751 mU/L, presumed stress-related. MRI, performed because of headache, showed a macroadenoma, 20 mm x 16 mm x 16 mm, with approx. 1 mm distance to chiasma. No visual deficit. No pituitary deficit. Because of typical headache, the patient was discussed in the interdisciplinary pituitary team, and admitted to surgery. The tumor was resected by transsphenoidal surgery in April 2005. There were no postoperative complications.

The first follow-up MRI after three months showed a residual tumor, without invasion of the cavernous sinus. Deficiencies in corticotroph and somatotroph function were revealed, and she was substituted with cortisone and growth hormone. Her headache was unfortunately persistent after operation.

She was initially followed closely because of growth hormone and cortisol replacement. MRI showed an increase in volume over time. However, the latest investigations have indicated a stabilization of tumor volume. She was referred to neurosurgical evaluation again in 2014, because of tumor growth. Her vision was intact, and a second surgery was postponed so far.

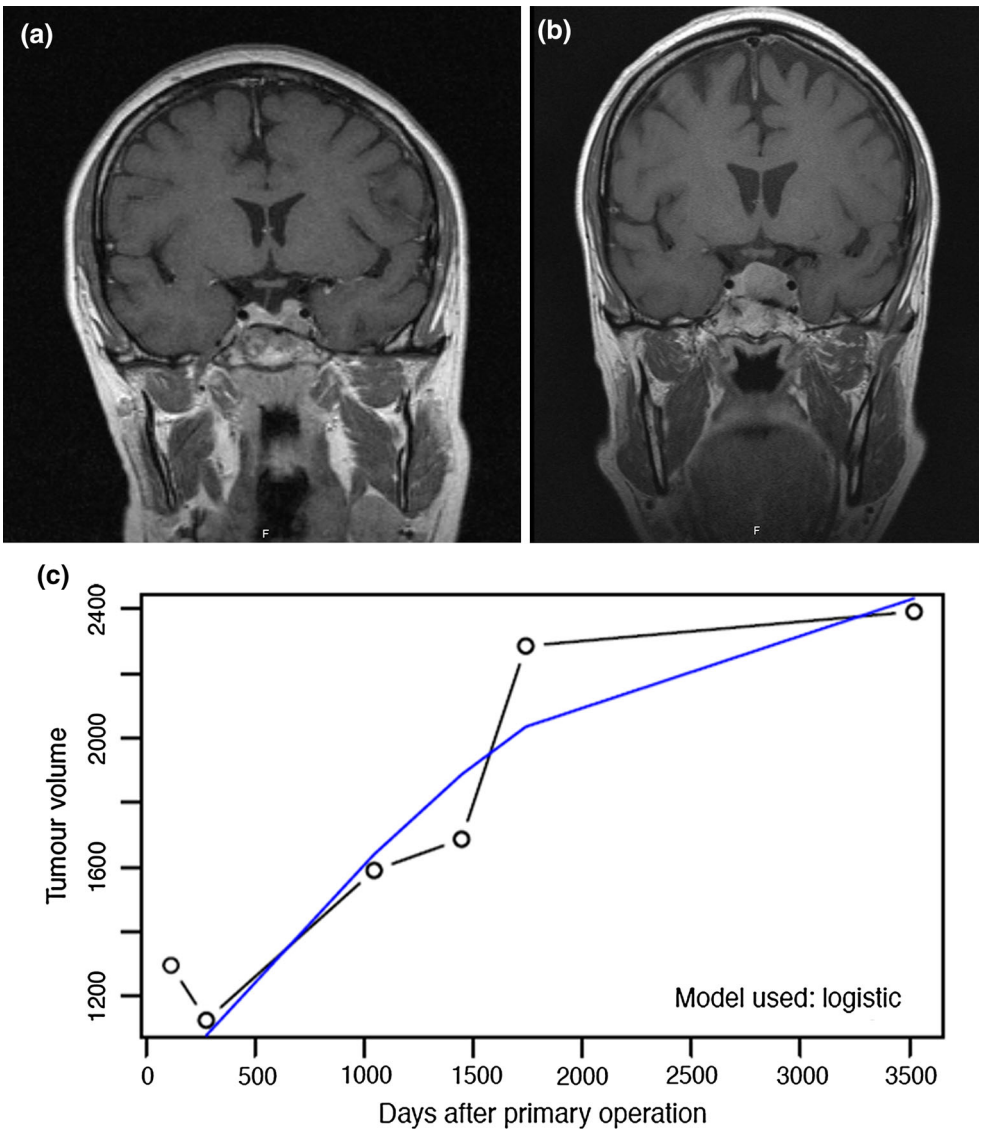


Fig. 1 MRI performed routinely after surgery, here illustrated by one-(Fig. 1**a**) and nine-(Fig. 1**b**) year postoperative MRI investigations. The *pictures* clearly show tumor growth. Figure 1**c** illustrates the patient's growth curve, which is congruent with a logistic growth pattern

observational study in Iceland spanning almost six decades demonstrated an overall prevalence of NFPA for 2012 of 43/100.000 inhabitants, NFPA being the next most prevalent diagnosed pituitary tumor. For the entire period, NFPAs were the most prevalent, comprising 43 % of all diagnosed adenomas. The standard incidence rate for PA increased during the observed period, estimated to be 5.8/100.000 by the end of the period [7]. The incidence rate and distribution seem to be comparable with recent estimates from the Swedish Pituitary Register Study,

demonstrating an overall incidence rate of PA of 3.9/100.000 per year [8]. Also here, NFPAs were the most common (54 %), followed by the hormone-secreting adenomas (i.e., prolactinomas (32 %), growth hormone producing (9 %), ACTH producing (4 %), and TSH producing (0.7 %)). Thus, it seems that the prevalence of NFPAs is fourfold higher than previously reported, suggesting that the tumors have an important burden on the Health Care System. Therefore, optimal resource distribution for both clinical care and research activities aiming to improve the outcome for these patients is needed [7, 9, 10].

Classification

Pituitary adenomas are classified into different systems based on the modalities of investigation. Radiologic investigations describe pituitary adenomas according to their size and invasiveness into surrounding structures. Histological investigations sub-classify the tumors by immunohistochemical staining (IHC) and define the level of atypia. The clinical course of the patient will assess the aggressiveness of the tumor [11]. A major challenge in diagnosing, treating, and following these patients is that there seems to be no reliable correlation between the radiological or histological characterization of the tumors and the clinical course.

Pituitary adenomas are also split into clinically functioning and non-functioning adenomas. The latter again divided into silent pituitary adenomas, staining immunohistochemically for one or several pituitary hormones but without hormonal secretion, and null-cell adenomas. Some tumors not manifesting symptoms may, however, have a low but detectable overproduction of hormones; further, challenging the classification of the tumors [12]. Identification of transcription factors to determine adenohypophyseal cell lineage as a supplement to hormone staining in the sub-classification of NFPAs has recently been suggested. This might give a more precise classification, in particular, for the hormone-negative, null-cell, adenomas [13].

WHO published criteria for atypical pituitary adenomas in 2004 according to mitotic activity, Ki-67 index, and p53 immunoreactivity [14]. A high Ki-67 value is associated with greater tumor size and an increased risk of tumor recurrence [15, 16]. Ki-67 is to date the most reliable cell proliferation marker [11]. It has, however, a low accuracy in prognosticating an aggressive clinical course [17], and there is a lack of standardization of method and sampling [11]. In recent years, Trouillas et al. proposed a new histopathological classification system taking size and IHC subtype, in addition to tumor grade based on proliferation rate and invasiveness, into account [17]. They found a significant difference between the grades related to the rate of recurrence/progression at the end of follow-up in their cohort. The effect of grading on recurrence differed between the subtypes of tumors [12].

In search for a reliable biomarker of aggressiveness, growth factors (e.g., FGFR4), proteolytic enzymes (e.g., MMPs), angiogenetic factors (e.g., VEGF, PTTG) in addition to the proliferation factors have been studied. However, more investigations in well-characterized cohorts are needed before these or other new markers can be introduced [11, 15]. A potential marker of aggressiveness is E-cadherin. Epithelial to mesenchymal transition (EMT) is a tissue phenotype modulation, characterized by disruption of cell contacts and enhanced motility. EMT is associated with the invasion and dissemination of cancer cells in several epithelial cancers [18]. E-cadherin is the main cell–cell adhesion contact in epithelial tissue, and down regulation of E-cadherin is the hallmark of EMT, leading to the destabilization of the cellular architecture. Previous studies have shown an association between EMT and aggressiveness of somatotroph and corticotroph pituitary adenomas [19–21]. So far, little has been described about growth rate and EMT in NFPAs.

Present and future therapies

Transsphenoidal surgery is the mainstay of treatment for large and symptomatic NFPAs, with an acceptable complication rate [22]. There are great differences between surgical outcomes with reported gross total removal ranging between 83 [23] and 19 % [24]. Postoperative irradiation is effective for residual tumors with growth potential, but at the price of an increased risk of hypopituitarism [25–27] and other possible, though more seldom, radiation induced long-term complications [28]. Fractionated radiation therapy or single-fraction radiosurgery (e.g., stereotactic gamma knife treatment) is the most common alternatives of irradiation [27, 29]. Novel techniques in both radiotherapy and radiosurgery are promising in increasing accuracy of the target tissue, while diminishing side effects [30]. Proton therapy has been hypothesized to be efficient while sparing adjacent radiation-sensitive tissue. There is, however, a lack of prospective, randomized controlled studies on the effect and studies on long-term complications [31, 32].

To date, there have been no large RCTs on medical treatment of NFPAs. For the functional pituitary tumors, two drug groups have proven effective, with an acceptable safety profile: dopamine agonists (DA) and somatostatin analogs (SA). Dopamine receptor subtype 2 is expressed in NFPAs both on mRNA and protein level [33]. DAs seem promising in achieving tumor stabilization, as

recently summarized in this journal [34]. A phase three RCT addressing the effect of cabergoline (DA) on change in tumor volume is currently recruiting participants [35].

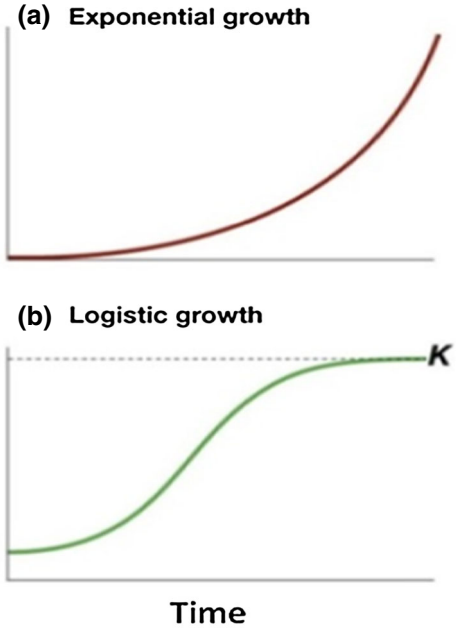
In somatotroph tumors, there is a correlation between the long-term effect of octreotide on IGF-1 and the IHC expression of somatostatin receptor (SSTR) 2 [36]. Octreotide has a high affinity for SSTR2, while the second-generation SA, pasireotide (SOM230) has a high affinity for SSTR1, SSTR2, SSTR3 and the highest affinity for SSTR5 [37]. The expressions of the various SSTRs in the tumors seem to be indicative for the effect of different SAs [38]. NFPAs express SSTRs [39, 40], but the expression of SSTR2 was found to be lower than in somatotroph adenomas [41]. This may partly explain the relatively disappointing results of octreotide. Most studies of octreotide on NFPAs have been of short duration and with relatively few patients [42], but the use of longer-acting octreotide and longer observations did not seem to improve the outcome [43].

Several studies have found a high expression of SSTR3 in NFPAs [40, 41], especially in null-cell adenomas [39] and silent gonadotroph adenomas [39, 44]. With this in mind, the evaluation of pasireotide as an alternative medical treatment of NFPAs is of great interest [45].

Aggressive pituitary adenomas and carcinomas are rare. Temozolomide (TMZ), a lipophilic alkylating agent, is a potential treatment alternative or supplement for this patient group and for tumors where tumor control is not achieved by conventional treatment [30, 46]. Available studies on this matter have included both functioning and non-functioning pituitary adenomas, the latter consisting of only a few cases [46, 47]. There is an ongoing initiative in Europe for collecting information on larger patient cohorts in respect to the use of TMZ [48].

Growth patterns

The progression rate of NFPAs is difficult to estimate. Some NFPAs show a slow growth and necessitate a long observation time, while others act more aggressively and invade the neighboring structures, thereby requiring rapid neurosurgical intervention to prevent long-term impairment on visual field or pituitary deficiency [3]. Information on tumor growth and behavior, before and after surgery, for this group of tumors is sparse [49, 50]. Annual surveillance by MRI for the first five postoperative years, thereafter MRI according to growth, residual tumor and/or clinical signs has been suggested [51]. Annual MRI follow-up has also been considered as cost-effective, although this varies substantially between regions [52]. To date, there are no data, to our knowledge, concluding when the right time to terminate surveillance of NFPAs neither after surgery nor conservatively treated [53–56]. Reddy et al. found that more than 20 % of relapses after surgery happened more than 10 years after the first operation. They also found a significant increase in rate of relapse if the residual tumor was present after surgery, and if the residual tumor was extra- rather than intra-sellar [24]. Some studies have found invasion of cavernous sinus to be predicative of future recurrence of NFPAs, though the results have been conflicting [54, 55, 57–60].



TVDT = Tumor volume doubling time

t = time of measurement 1 and 2

V = Volume of tumor at time 1 and 2.

$$\mathrm{TVDT} = \frac{(t_2 - t_1)\log 2}{\log(\frac{V2}{V1})}$$

TVDT is calculated by dividing the product of the logarithm of 2 and time interval with the logarithm of the volume quotient. The formula for TVDT assumes an exponential growth curve for tumor growth.

Fig. 2 Two different growth patterns being applicable for pituitary adenomas [61]. Applying TVDT and thereby the exponential growth pattern will be the most conservative approach. An estimate of TVDT or an indication of logistic growth would markedly reduce the number of investigations as compared current management of patients

Information and understanding of adenoma growth kinetics (i.e., linear, logistic or exponential growth) collaborated with data about tumor biology would substantially enhance our clinical acquaintance of tumor behavior and help to adjust and individualize MRI scanning protocols and follow-up (Fig. 2) [61]. The so far only published systematic study investigating specific growth kinetics of NFPAs, although with a limited number of patients ($n = 15$), concluded that the linear growth model is not suitable and that an exponential or a logistic growth model is more accurate to describe the growth kinetics of NFPAs [61].

The different subgroups of NFPAs show different clinical behaviors, and some are known to be more aggressive than others [3, 62]. Balogun et al. found in their cohort of null-cell and silent gonadotroph adenomas a difference in growth behavior prior to and after surgery between the two subgroups [63]. Brochier et al. showed a significant difference in relapse rate between immunohistochemical subgroups [64]. Thus, it seems reasonable that non-functioning pituitary adenomas are a heterogeneous group of tumors with different growth patterns, and more information is needed to better describe the behavior of these tumors.

Conclusion

Non-functioning pituitary adenomas are a heterogeneous group of tumors, with a variety of clinical manifestations and courses. To date, there is no known credible marker of aggressive growth or behavior, making the monitoring of the patients a challenge. Some studies show a latent growth potential of these tumors, and suggest a prolonged follow-up. More information on growth patterns with constituent markers are needed to tailor the care of this patient group. Studies characterizing the membrane receptors of NFPAs have shown promising results, which may give rise to the development of medical treatment.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest. The patient case is given with permission from the patient.

References

1. E.D. Aflorei, M. Korbonits, Epidemiology and etiopathogenesis of pituitary adenomas. J. Neurooncol. **117**(3), 379–394 (2014). doi:10.1007/s11060-013-1354-5
2. G. Vargas, B. Gonzalez, C. Ramirez, A. Ferreira, E. Espinosa, V. Mendoza, G. Guinto, B. Lopez-Felix, E. Zepeda, M. Mercado, Clinical characteristics and treatment outcome of 485 patients with nonfunctioning pituitary macroadenomas. Int. J. Endocrinol. **2015**, 756069 (2015). doi:10.1155/2015/756069
3. O. Cooper, S. Melmed, Subclinical hyperfunctioning pituitary adenomas: the silent tumors. Best practice & research. Clinical. Endocrinol. Metab **26**(4), 447–460 (2012). doi:10.1016/j.beem.2012.01.002
4. G. Carosi, E. Malchiodi, E. Ferrante, E. Sala, E. Verrua, E. Profka, C. Giavoli, M. Filopanti, P. Beck-Peccoz, A. Spada, G. Mantovani, Hypothalamic-pituitary axis in non-functioning pituitary adenomas: focus on the prevalence of isolated central hypoadrenalism. Neuroendocrinology **102**(4), 267–273 (2015). doi:10.1159/000430815
5. O. Vierimaa, M. Georgitsi, R. Lehtonen, P. Vahteristo, A. Kokko, A. Raitila, K. Tuppurainen, T.M. Ebeling, P.I. Salmela, R. Paschke, S. Gundogdu, E. De Menis, M.J. Makinen, V. Launonen, A. Karhu, L.A. Aaltonen, Pituitary adenoma predisposition caused by germline mutations in the AIP gene. Science **312**(5777), 1228–1230 (2006). doi:10.1126/science.1126100
6. C. Esteves, C. Neves, L. Augusto, J. Menezes, J. Pereira, I. Bernardes, J. Fonseca, D. Carvalho, Pituitary incidentalomas: analysis of a neuroradiological cohort. Pituitary **18**(6), 777–781 (2015). doi:10.1007/s11102-015-0652-7
7. T.T. Agustsson, T. Baldvinsdottir, J.G. Jonasson, E. Olafsdottir, V. Steinthorsdottir, G. Sigurdsson, A.V. Thorsson, P.V. Carroll, M. Korbonits, R. Benediktsson, The epidemiology of pituitary adenomas in Iceland, 1955–2012: a nationwide population-based study. Eur. J. Endocrinol. **173**(5), 655–664 (2015). doi:10.1530/eje-15-0189
8. A. Tjornstrand, K. Gunnarsson, M. Evert, E. Holmberg, O. Ragnarsson, T. Rosen, Filipsson Nystrom, H.: the incidence rate of pituitary adenomas in western Sweden for the period 2001–2011. Eur. J. Endocrinol. **171**(4), 519–526 (2014). doi:10.1530/eje-14-0144
9. A. Fernandez, N. Karavitaki, J.A. Wass, Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). Clin. Endocrinol. (Oxf) **72**(3), 377–382 (2010). doi:10.1111/j.1365-2265.2009.03667.x
10. A.F. Daly, M. Rixhon, C. Adam, A. Dempegioti, M.A. Tichomirowa, A. Beckers, High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. J. Clin. Endocrinol. Metab. **91**(12), 4769–4775 (2006). doi:10.1210/jc.2006-1668
11. A. Di Ieva, F. Rotondo, L.V. Syro, M.D. Cusimano, K. Kovacs, Aggressive pituitary adenomas–diagnosis and emerging treatments. Nat. Rev. Endocrinol. **10**(7), 423–435 (2014). doi:10.1038/nrendo.2014.64
12. S.E. Mayson, P.J. Snyder, Silent pituitary adenomas. Endocrinol. Metab. Clin. North Am. **44**(1), 79–87 (2015). doi:10.1016/j.ecl.2014.11.001
13. H. Nishioka, N. Inoshita, O. Mete, S.L. Asa, K. Hayashi, A. Takeshita, N. Fukuhara, M. Yamaguchi-Okada, Y. Takeuchi, S. Yamada, The complementary role of transcription factors in the accurate diagnosis of clinically nonfunctioning pituitary adenomas. Endocr. Pathol. **26**(4), 349–355 (2015). doi:10.1007/s12022-015-9398-z
14. R. DeLellis, P. Heitz, World Health Organization Classification of Tumours: Tumours of Endocrine Organs. IARC PRess, Lyon (2004)
15. C. Ramirez, S. Cheng, G. Vargas, S.L. Asa, S. Ezzat, B. Gonzalez, L. Cabrera, G. Guinto, M. Mercado, Expression of Ki-67, PTTG1, FGFR4, and SSTR 2, 3, and 5 in nonfunctioning pituitary adenomas: a high throughput TMA, immunohistochemical study. J. Clin. Endocrinol. Metab. **97**(5), 1745–1751 (2012). doi:10.1210/jc.2011-3163
16. A. Righi, P. Agati, A. Sisto, G. Frank, M. Faustini-Fustini, R. Agati, D. Mazzatenta, A. Farnedi, F. Menetti, G. Marucci, M.P. Foschini, A classification tree approach for pituitary adenomas.

Hum. Pathol. **43**(10), 1627–1637 (2012). doi:10.1016/j.humpath.2011.12.003
17. J. Trouillas, P. Roy, N. Sturm, E. Dantony, C. Cortet-Rudelli, G. Viennet, J.F. Bonneville, R. Assaker, C. Auger, T. Brue, A. Cornelius, H. Dufour, E. Jouanneau, P. Francois, F. Galland, F. Mougel, F. Chapuis, L. Villeneuve, C.A. Maurage, D. Figarella-Branger, G. Raverot, A. Barlier, M. Bernier, F. Bonnet, F. Borson-Chazot, G. Brassier, S. Caulet-Maugendre, O. Chabre, P. Chanson, J.F. Cottier, B. Delemer, E. Delgrange, L. Di Tommaso, S. Eimer, S. Gaillard, M. Jan, J.J. Girard, V. Lapras, H. Loiseau, J.G. Passagia, M. Patey, A. Penfornis, J.Y. Poirier, G. Perrin, A. Tabarin, A new prognostic clinicopathological classification of pituitary adenomas: a multicentric case-control study of 410 patients with 8 years post-operative follow-up. Acta Neuropathol. **126**(1), 123–135 (2013). doi:10.1007/s00401-013-1084-y
18. M. Guarino, B. Rubino, G. Ballabio, The role of epithelial-mesenchymal transition in cancer pathology. Pathology **39**(3), 305–318 (2007). doi:10.1080/00313020701329914
19. S.L. Fougner, T. Lekva, O.C. Borota, J.K. Hald, J. Bollerslev, J.P. Berg, The expression of E-cadherin in somatotroph pituitary adenomas is related to tumor size, invasiveness, and somatostatin analog response. J. Clin. Endocrinol. Metab. **95**(5), 2334–2342 (2010). doi:10.1210/jc.2009-2197
20. T. Lekva, J.P. Berg, S.L. Fougner, O.K. Olstad, T. Ueland, J. Bollerslev, Gene expression profiling identifies ESRP1 as a potential regulator of epithelial mesenchymal transition in somatotroph adenomas from a large cohort of patients with acromegaly. J. Clin. Endocrinol. Metab. **97**(8), E1506–E1514 (2012). doi:10.1210/jc.2012-1760
21. J.A. Evang, J.P. Berg, O. Casar-Borota, T. Lekva, M.K. Kringen, J. Ramm-Pettersen, J. Bollerslev, Reduced levels of E-cadherin correlate with progression of corticotroph pituitary tumours. Clin. Endocrinol. (Oxf) **75**(6), 811–818 (2011). doi:10.1111/j.1365-2265.2011.04109.x
22. H. Halvorsen, J. Ramm-Pettersen, R. Josefsen, P. Ronning, S. Reinlie, T. Meling, J. Berg-Johnsen, J. Bollerslev, E. Helseth, Surgical complications after transsphenoidal microscopic and endoscopic surgery for pituitary adenoma: a consecutive series of 506 procedures. Acta Neurochir. (Wien) **156**(3), 441–449 (2014). doi:10.1007/s00701-013-1959-7
23. J. Honegger, U. Ernemann, T. Psaras, B. Will, Objective criteria for successful transsphenoidal removal of suprasellar nonfunctioning pituitary adenomas. A prospective study. Acta Neurochir. **149**(1), 21–29 (2007). doi:10.1007/s00701-006-1044-6
24. R. Reddy, S. Cudlip, J.V. Byrne, N. Karavitaki, J.A. Wass, Can we ever stop imaging in surgically treated and radiotherapy-naive patients with non-functioning pituitary adenoma? Eur. J. Endocrinol. **165**(5), 739–744 (2011). doi:10.1530/eje-11-0566
25. A. Colao, G. Cerbone, P. Cappabianca, D. Ferone, A. Alfieri, F. Di Salle, A. Faggiano, B. Merola, E. de Divitiis, G. Lombardi, Effect of surgery and radiotherapy on visual and endocrine function in nonfunctioning pituitary adenomas. J. Endocrinol. Invest. **21**(5), 284–290 (1998). doi:10.1007/bf03350330
26. D. Ding, C.P. Yen, R.M. Starke, C.C. Lee, J.P. Sheehan, Unyielding progress: recent advances in the treatment of central nervous system neoplasms with radiosurgery and radiation therapy. J. Neurooncol. **119**(3), 513–529 (2014). doi:10.1007/s11060-014-1501-7
27. G. Ntali, N. Karavitaki, Efficacy and complications of pituitary irradiation. Endocrinol. Metab. Clin. North Am. **44**(1), 117–126 (2015). doi:10.1016/j.ecl.2014.10.009
28. N.C. van Varsseveld, C.C. van Bunderen, D.H. Ubachs, A.A. Franken, H.P. Koppeschaar, A.J. van der Lely, M.L. Drent, Cerebrovascular events, secondary intracranial tumors, and mortality after radiotherapy for nonfunctioning pituitary adenomas: a subanalysis from the dutch national registry of growth hormone treatment in adults. J. Clin. Endocrinol. Metab. **100**(3), 1104–1112 (2015). doi:10.1210/jc.2014-3697
29. D. Ding, R.M. Starke, J.P. Sheehan, Treatment paradigms for pituitary adenomas: defining the roles of radiosurgery and radiation therapy. J. Neurooncol. **117**(3), 445–457 (2014). doi:10.1007/s11060-013-1262-8
30. E. Chatzellis, K.I. Alexandraki, I.I. Androulakis, G. Kaltsas, Aggressive pituitary tumors. Neuroendocrinology **101**(2), 87–104 (2015). doi:10.1159/000371806
31. S.E. Combs, K. Kessel, D. Habermehl, T. Haberer, O. Jakel, J. Debus, Proton and carbon ion radiotherapy for primary brain tumors and tumors of the skull base. Acta Oncol. **52**(7), 1504–1509 (2013). doi:10.3109/0284186x.2013.818255
32. D.A. Wattson, S.K. Tanguturi, D.Y. Spiegel, A. Niemierko, B.M. Biller, L.B. Nachtigall, M.R. Bussiere, B. Swearingen, P.H. Chapman, J.S. Loeffler, H.A. Shih, Outcomes of proton therapy for patients with functional pituitary adenomas. Int. J. Radiat. Oncol. Biol. Phys. **90**(3), 532–539 (2014). doi:10.1016/j.ijrobp.2014.06.068
33. Vieira Neto, L. Wildemberg, L.E. Moraes, A.B. Colli, L.M. Kasuki, N.V. Marques, E.L. Gasparetto, M. Takiya, C.M. Gadelha, Dopamine receptor subtype 2 expression profile in nonfunctioning pituitary adenomas and in vivo response to cabergoline therapy. Clin. Endocrinol. (Oxf) **82**(5), 739–746 (2015). doi:10.1111/cen.12684
34. Y. Greenman, N. Stern, Optimal management of non-functioning pituitary adenomas. Endocrine **50**(1), 51–55 (2015). doi:10.1007/s12020-015-0685-8
35. St. Olavs Hospital; Norwegian University of Science Technology: Dopamine agonist treatment of non-functioning pituitary adenomas (NFPAs)—a randomized controlled trial. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US)
36. S.L. Fougner, O.C. Borota, J.P. Berg, J.K. Hald, J. Ramm-Pettersen, J. Bollerslev, The clinical response to somatostatin analogues in acromegaly correlates to the somatostatin receptor subtype 2a protein expression of the adenoma. Clin. Endocrinol. (Oxf) **68**(3), 458–465 (2008). doi:10.1111/j.1365-2265.2007.03065.x
37. C. Bruns, I. Lewis, U. Briner, G. Meno-Tetang, G. Weckbecker, SOM230: a novel somatostatin peptidomimetic with broad somatotropin release inhibiting factor (SRIF) receptor binding and a unique antisecretory profile. Eur. J. Endocrinol. **146**(5), 707–716 (2002)
38. D. Iacovazzo, E. Carlsen, F. Lugli, S. Chiloiro, S. Piacentini, A. Bianchi, A. Giampietro, M. Mormando, A.J. Clear, F. Doglietto, C. Anile, G. Maira, L. Lauriola, G. Rindi, F. Roncaroli, A. Pontecorvi, M. Korbonits, L. De Marinis, Factors predicting pasireotide responsiveness in somatotroph pituitary adenomas resistant to first-generation somatostatin analogues: an immunohistochemical study. Eur. J. Endocrinol. **174**(2), 241–250 (2016). doi:10.1530/eje-15-0832
39. H. Nishioka, K. Tamura, H. Iida, M. Kutsukake, A. Endo, Y. Ikeda, J. Haraoka, Co-expression of somatostatin receptor subtypes and estrogen receptor-alpha mRNAs by non-functioning pituitary adenomas in young patients. Mol. Cell. Endocrinol. **331**(1), 73–78 (2011). doi:10.1016/j.mce.2010.08.011
40. G.F. Taboada, R.M. Luque, W. Bastos, R.F. Guimaraes, J.B. Marcondes, L.M. Chimelli, R. Fontes, P.J. Mata, P.N. Filho, D.P. Carvalho, R.D. Kineman, M.R. Gadelha, Quantitative analysis of somatostatin receptor subtype (SSTR1-5) gene expression levels in somatotropinomas and non-functioning pituitary adenomas. Eur. J. Endocrinol. **156**(1), 65–74 (2007). doi:10.1530/eje.1.02313
41. Vieria Neto, L., Wildemberg, L.E., Colli, L.M., Kasuki, L., Marques, N.V., Moraes, A.B., Gasparetto, E.L., Takiya, C.M.,

Castro, M., Gadelha, M.R.: zAC1 and SSTR2 are downregulated in non-functioning pituitary adenomas but not in somatotropinomas. PLoS ONE **8**(10), e77406 (2013). doi:10.1371/journal.pone.0077406
42. M. Gasperi, L. Petrini, R. Pilosu, M. Nardi, A. Marcello, F. Mastio, L. Bartalena, E. Martino, Octreotide treatment does not affect the size of most non-functioning pituitary adenomas. J. Endocrinol. Invest. **16**(7), 541–543 (1993). doi:10.1007/bf03348901
43. A. Fusco, A. Giampietro, A. Bianchi, V. Cimino, F. Lugli, S. Piacentini, M. Lorusso, A. Tofani, G. Perotti, L. Lauriola, C. Anile, G. Maira, A. Pontecorvi, L. De Marinis, Treatment with octreotide LAR in clinically non-functioning pituitary adenoma: results from a case-control study. Pituitary **15**(4), 571–578 (2012). doi:10.1007/s11102-011-0370-8
44. M. Lee, A. Lupp, N. Mendoza, N. Martin, R. Beschorner, J. Honegger, J. Schlegel, T. Shively, E. Pulz, S. Schulz, F. Roncaroli, N.S. Pellegata, SSTR3 is a putative target for the medical treatment of gonadotroph adenomas of the pituitary. Endocr. Relat. Cancer **22**(1), 111–119 (2015). doi:10.1530/erc-14-0472
45. Novartis, P., Novartis: Evaluate the Efficacy and Safety of Pasireotide LAR on the Treatment of Patients With Clinically Non-Functioning Pituitary Adenoma. In. Bethesda (MD): National Library of Medicine (US) (2016)
46. D. Bengtsson, H.D. Schroder, M. Andersen, D. Maiter, K. Berinder, Feldt Rasmussen, U., Rasmussen, A.K., Johannsson, G., Hoybye, C., van der Lely, A.J., Petersson, M., Ragnarsson, O., Burman, P.: long-term outcome and MGMT as a predictive marker in 24 patients with atypical pituitary adenomas and pituitary carcinomas given treatment with temozolomide. J. Clin. Endocrinol. Metabo. **100**(4), 1689–1698 (2015). doi:10.1210/jc.2014-4350
47. G. Raverot, F. Castinetti, E. Jouanneau, I. Morange, D. Figarella-Branger, H. Dufour, J. Trouillas, T. Brue, Pituitary carcinomas and aggressive pituitary tumours: merits and pitfalls of temozolomide treatment. Clin. Endocrinol. (Oxf) **76**(6), 769–775 (2012). doi:10.1111/j.1365-2265.2012.04381.x
48. G. Raverot, P. Burman, A. McCormack, S. Petersenn, V. Popovic-Brkic, J. Trouillas, ESE Survey on Aggressive Pituitary Tumors. http://www.ese-hormones.org/professional/
49. Y. Chen, C.D. Wang, Z.P. Su, Y.X. Chen, L. Cai, Q.C. Zhuge, Z.B. Wu, Natural history of postoperative nonfunctioning pituitary adenomas: a systematic review and meta-analysis. Neuroendocrinology **96**(4), 333–342 (2012). doi:10.1159/000339823
50. E. Monsalves, S. Larjani, B. Loyola Godoy, K. Juraschka, F. Carvalho, W. Kucharczyk, A. Kulkarni, O. Mete, F. Gentili, S. Ezzat, G. Zadeh, Growth patterns of pituitary adenomas and histopathological correlates. J. Clin. Endocrinol. Metab. **99**(4), 1330–1338 (2014). doi:10.1210/jc.2013-3054
51. C. Cortet-Rudelli, J.F. Bonneville, F. Borson-Chazot, L. Clavier, B. Coche Dequeant, R. Desailloud, D. Maiter, V. Rohmer, J.L. Sadoul, E. Sonnet, P. Toussaint, P. Chanson, Post-surgical management of non-functioning pituitary adenoma. Ann Endocrinol (Paris) **76**(3), 228–238 (2015). doi:10.1016/j.ando.2015.04.003
52. H.M. Kistka, R.A. Kasl, A. Nayeri, A.L. Utz, K.D. Weaver, L.B. Chambless, Imaging of resected nonfunctioning pituitary adenomas: the cost of surveillance. J. Neurol. Surg. **76**(5), 344–350 (2015). doi:10.1055/s-0035-1549307
53. P.U. Freda, A.M. Beckers, L. Katznelson, M.E. Molitch, V.M. Montori, K.D. Post, M.L. Vance, Pituitary incidentaloma: an endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. **96**(4), 894–904 (2011). doi:10.1210/jc.2010-1048
54. G. Soto-Ares, C. Cortet-Rudelli, R. Assaker, A. Boulinguez, C. Dubest, D. Dewailly, J.P. Pruvo, MRI protocol technique in the optimal therapeutic strategy of non-functioning pituitary adenomas. Eur. J. Endocrinol. **146**(2), 179–186 (2002)
55. E.P. O'Sullivan, C. Woods, N. Glynn, L.A. Behan, R. Crowley, P. O'Kelly, D. Smith, C.J. Thompson, A. Agha, The natural history of surgically treated but radiotherapy-naive nonfunctioning pituitary adenomas. Clin. Endocrinol. (Oxf) **71**(5), 709–714 (2009). doi:10.1111/j.1365-2265.2009.03583.x
56. N. Lenders, S. Ikeuchi, A.W. Russell, K.K. Ho, J.B. Prins, W.J. Inder, Longitudinal evaluation of the natural history of conservatively managed non-functioning pituitary adenomas. Clin. Endocrinol. (Oxf) (2015). doi:10.1111/cen.12879
57. Y. Greenman, G. Ouaknine, I. Veshchev, G. Reider II, Y. Segev, N. Stern, Postoperative surveillance of clinically nonfunctioning pituitary macroadenomas: markers of tumour quiescence and regrowth. Clin. Endocrinol. (Oxf) **58**(6), 763–769 (2003)
58. M. Losa, P. Mortini, R. Barzaghi, P. Ribotto, M.R. Terreni, S.B. Marzoli, S. Pieralli, M. Giovanelli, Early results of surgery in patients with nonfunctioning pituitary adenoma and analysis of the risk of tumor recurrence. J. Neurosurg. **108**(3), 525–532 (2008). doi:10.3171/jns/2008/108/3/0525
59. E.F. Chang, G. Zada, S. Kim, K.R. Lamborn, A. Quinones-Hinojosa, J.B. Tyrrell, C.B. Wilson, S. Kunwar, Long-term recurrence and mortality after surgery and adjuvant radiotherapy for nonfunctional pituitary adenomas. J. Neurosurg. **108**(4), 736–745 (2008). doi:10.3171/jns/2008/108/4/0736
60. F. Roelfsema, N.R. Biermasz, A.M. Pereira, Clinical factors involved in the recurrence of pituitary adenomas after surgical remission: a structured review and meta-analysis. Pituitary **15**(1), 71–83 (2012). doi:10.1007/s11102-011-0347-7
61. J. Honegger, S. Zimmermann, T. Psaras, M. Petrick, M. Mittelbronn, U. Ernemann, M. Reincke, K. Dietz, Growth modelling of non-functioning pituitary adenomas in patients referred for surgery. Eur. J. Endocrinol. **158**(3), 287–294 (2008). doi:10.1530/eje-07-0502
62. S. Yamada, K. Ohyama, M. Taguchi, A. Takeshita, K. Morita, K. Takano, T. Sano, A study of the correlation between morphological findings and biological activities in clinically nonfunctioning pituitary adenomas. Neurosurgery **61**(3), 580–584 (2007). doi:10.1227/01.neu.0000290906.53685.79
63. J.A. Balogun, E. Monsalves, K. Juraschka, K. Parvez, W. Kucharczyk, O. Mete, F. Gentili, G. Zadeh, Null cell adenomas of the pituitary gland: an institutional review of their clinical imaging and behavioral characteristics. Endocr. Pathol. **26**(1), 63–70 (2015). doi:10.1007/s12022-014-9347-2
64. S. Brochier, F. Galland, M. Kujas, F. Parker, S. Gaillard, C. Raftopoulos, J. Young, O. Alexopoulou, D. Maiter, P. Chanson, Factors predicting relapse of nonfunctioning pituitary macroadenomas after neurosurgery: a study of 142 patients. Eur. J. Endocrinol. **163**(2), 193–200 (2010). doi:10.1530/eje-10-0255