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Pituitary Tumors

Prognostic Indicators

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Many factors influence the proliferation of pituitary adenomas: angiogenesis, apoptosis, growth factors, oncogenes, tumor suppressor genes, and hormone receptors. These elements can be demonstrated by immunohistochemistry and/or molecular pathology but no single factor can be used for determination of biological behavior resp. prognosis. Pituitary adenomas can be enclosed or invasive and may be very large or may be microadenomas, but the most important point for prognosis is the total resection in the first or second surgery or the reaction on treatments by drugs. Especially for residual tumor tissue proliferation, markers are important because they may indicate the growth rate and the aggressiveness of the tumor. Radiation therapy is indicated in many of these recurrent tumors and can improve the prognosis.

Key Words: Inactive adenoma; pituitary; tumor; adenoma; atypical adenoma; carcinoma.

Introduction

According to the WHO classification 2004 *(1)* pituitary tumors deriving from adenohypophysial parenchymal cells are classified in typical adenomas, atypical adenomas, and carcinomas. By far the most common tumors are monomorphic adenomas, whereas atypical adenomas being defined by a Ki-67 index of 3% or more account for about 5% of tumors. Pituitary carcinomas must show metastases. Brain invasion as the only criterion of malignancy is not generally accepted. Although defined as benign tumors, nearly 50% of pituitary adenomas invade surroundings tissues (invasive adenomas) *(2)*.

The prognosis of pituitary tumors depends not only on histopathologic classification or immunohistologic proliferation markers but also on their size and invasiveness and their operability or sensitivity for drugs. Molecular pathology has up to now a small or limited value for evaluation of prognosis.

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Enclosed and Invasive Adenomas

Enclosed adenomas have a sharp border to the remaining pituitary tissue (Fig. 1) but also to the sellar bone, the cavernous sinus, and the diaphragm, whereas invasive adenomas grow into the sellar bone (Fig. 2), the sphenoid sinus, or the cavernous sinus and diaphragm. The rate of invasiveness is different in the various adenoma types (Table 1). In correlation to proliferation markers, Ki-67 index is generally higher in invasive adenomas *(3,4)* and p53 positive nuclei may be demonstrated in invasive adenomas but cannot be found in enclosed adenomas *(3,5,6)*.

The principal significance of invasion is the possible persistence of tumor tissue after surgical resection. In one study *(7)* the survival rate at 6 yr postsurgery was slightly but significantly decreased for patients with dural invasion. Invasiveness is unimportant for prognosis if the tumor can be completely surgically resected. In cases that cannot be cured by surgery invasiveness is accompanied by regrowth of adenoma and poor prognosis.

Adenoma Types

The adenomas secreting GH and inducing acromegaly (densely granulated GH cell adenoma, sparsely granulated GH cell adenoma, mixed GH/Prolactin cell adenoma, mammosomatotroph adenoma) do not appear to have a different prognosis in correlation with the adenoma type, although the densely granulated GH cell adenoma shows an enhanced reduction of GH levels in response to octreotide in comparison to the sparsely granulated adenoma type *(8)*.

According to the adenomas in hyperprolactinemia (sparsely granulated prolactin cell adenoma, densely granulated prolactin cell adenoma, acidophil stem cell adenoma), the rare acidophil stem cell adenoma is a more aggressive and infiltrative tumor recurring more often than other types. It appears not to be suppressible by bromocriptine *(9)*.

ACTH-secreting tumors in Cushing's disease or Nelson's syndrome are densely or sparsely granulated ACTH cell adenomas. Differences in prognosis between both subtypes are not reported.

Adenomas with TSH excess are generally more aggressive and invasive *(10)* than most other adenoma types.

Most clinically inactive adenomas are gonadotrophic adenomas, null cell adenomas, or oncocytic adenomas *(10, 11)*. According to their types they do not differ in prognosis *(3,11)*. Silent ACTH cell adenomas of densely granulated

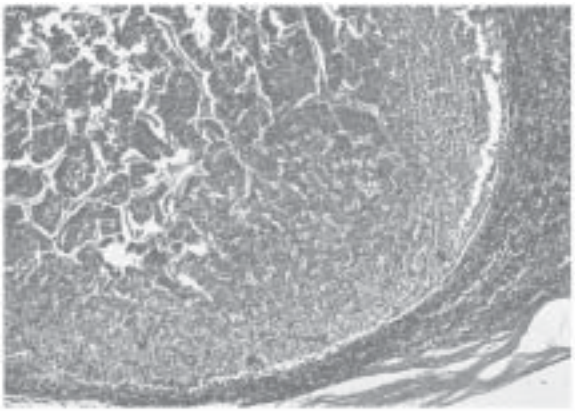

Fig. 1. Oncocytic adenoma sharply bordered to the ajacent anterior pituitary. Hematoxylin–eosin.

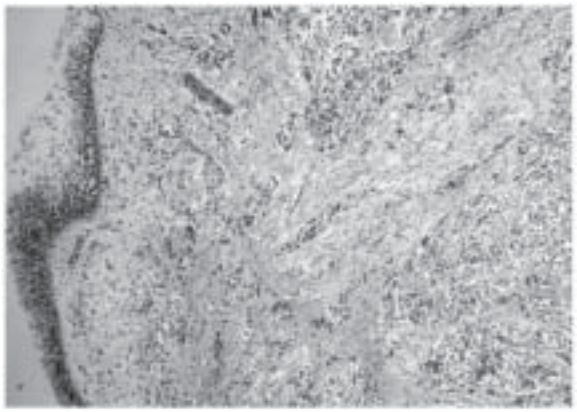

Fig. 2. Sparsely granulated GH cell adenoma invading the mucosa of sphenoid sinus. Hematoxylin–eosin.

Table 1
Rate of Invasiveness of Surgically Resected Pituitary Adenomas *(90)*

Adenoma type	Rate of macroadenomas (>1.0 cm)	Rate of invasiveness
Densely granulated GH-cell adenoma	86%	50%
Sparsely granulated GH-cell adenoma	52%	50%
Densely granulated prolactin-cell adenoma	74%	52%
Sparsely granulated prolactin-cell adenoma	50%	
Mixed GH/prolactin-cell adenoma	74%	31%
Mammosomatotroph adenoma	50%	≈30%
Acidophil stem cell adenoma	100% (?)	100% (?)
Densely and sparsely granulated ACTH cell adenoma		
Cushing	13%	15%
Nelson's syndrome	100%	82%
Inactive	100%	82%
Crooke's cell adenoma	75%	85%
TSH cell adenoma	100% (?)	100% (?)
FSH/LH cell adenoma	95%	95%
Null cell adenoma	95%	42%
Oncocytic adenoma	95%	?
Plurihormonal adenoma	75%	52%
Silent adenoma (subtype III)	100% (?)	100% (?)

type (type I) or sparsely granulated type (type II) are usually more aggressive and recur more frequently than adenomas associated with hypercorticism *(1)* or other inactive adenomas.

An especially remarkable plurihormonal tumor is the silent subtype 3 adenoma *(1)* that often shows highly invasive lesions with suprasellar and parasellar extension. The histopathology of this adenoma type is characterized by strong pleomorphism and increased mitoses. Many combinations of pituitary hormone expressions can be found in these adenomas *(1)*. Its prognosis is characterized by the highly infilrative growth and the high recurrence rate.

Postmortem pituitaries of unselected autopsy series contain mostly very small adenomas (Fig. 3) in about 10% of cases *(12)* (Table 2). Most of these adenomas appear to have no biological significance but we do not know the long-term prognosis and outcome of these tumors if they have had the opportunity to develop further. Although most adenoma types are represented in those collections, aggressive adenomas especially acidophil stem cell adenomas and silent type 3 adenomas are not included in the series (Table 2).

Size of Tumors

The size of adenomas correlates with the type of adenoma: endocrine active tumors are generally smaller than inactive tumors because, due to the endocrine hyperfunction, the active adenomas are diagnosed in an earlier stage,

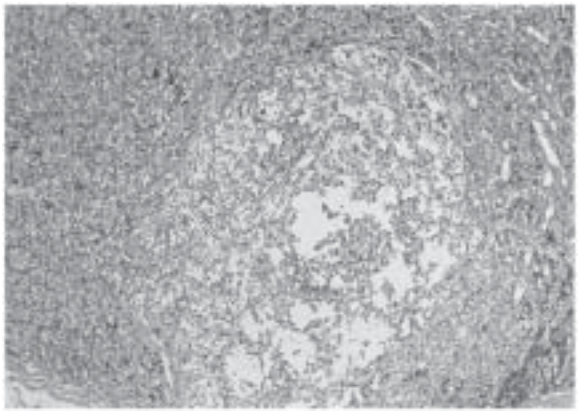

Fig. 3. Small null cell adenoma in postmortem pituitary. PAS reaction–hematoxylin.

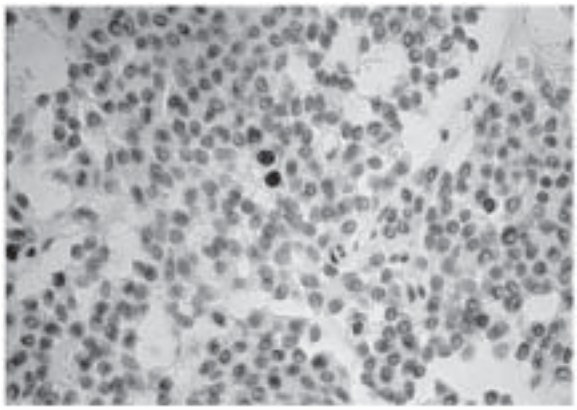

Fig. 4. Oncocytic adenoma with some MiB-1-positive nuclei. MiB-1 immunoreaction, ABC, hematoxlin.

Table 2
Adenomas in Postmortem Pituitaries[a]

Adenoma type	Number	Percentage
GH-cell adenoma, densely granulated	2	1.2
GH-cell adenoma, sparsely granulated	2	1.2
Prolactin-cell adenoma, sparsely granulated	60	35.7
ACTH-cell adenoma, densely granulated	13	7.7
ACTH-cell adenoma, sparsely granulated	10	6.0
Crooke's cell adenoma	1	0.6
FSH/LH cell adenoma	3	1.8
Alpha-subunit-only adenoma	1	0.6
Plurihormonal adenoma	6	3.6
Null cell adenoma	42	25.0
Oncocytic adenoma	19	11.3
Unclassified adenoma	6	3.6
Total	165	100.0

[a]Unselected series of 1658 autopsies, adenoma incidence 10.0% *(12)*.

whereas many inactive adenomas are only found when visual defects develop due to suprasellar growth.

Total resection of smaller tumors is more often possible than in larger tumors *(13)*, which also recur more frequent *(14)*.

Angiogenesis

Angiogenesis has been shown to be related to tumor behavior, prognosis, and response to treatment in many different tumor types. Pituitary adenomas show a significantly lower microvascular density than normal pituitary tissue. Invasive prolactinomas were significantly more vascular than non-invasive tumors. Surgical cure was found to be more likely in macroprolactinomas and in ACTH-secreting tumors with lower microvascular density *(15)*. On the other hand, although microvessel density is lower in pituitary adenomas than in normal gland, pituitary carcinomas show an increased microvessel density *(16)*.

Proliferation of Tumors

For evaluation of proliferative activity of pituitary tumors two important methods can be used: counting mitoses or immunostaining of nuclei for proliferation markers or for cell cycle inhibitors.

Number of Mitoses

In most adenomas mitoses are only very sparse or lacking but if they are demonstrable they are a good indicator of more rapid tumor growth.

Ki-67 / MiB-1

The most important proliferation marker Ki-67 is expressed in G1, S, G2, and M phases of the cell cycle. In an early study of 1987 *(17)*, biopsy specimens of 31 pituitary adenomas representing all major endocrine types harbored immunoreactive nuclei to Ki-67 ranging from 0.1% to 3.7%. Low values (0.1–1.0%) were present in 11 endocrine-inactive adenomas and higher values (1.1–1.5%) were found in 6 acromegalic patients. The percentages of Ki-67–positive cells in 12 prolactinomas and 2 adenomas from patients with Cushing's disease covered the entire range (0.1–3.7%). Preoperative bromocriptine treatment of prolactinomas did not influence Ki-67 expression.

In a more recent study *(4)* Ki-67 (MiB-1) was positive in 139 of 159 adenomas (87%). The Ki-67 index ranged from 0.16% to 15.48% (mean = 1.22 ± 2.09%) and was higher in ACTH-secreting adenomas. Invasive pituitary adenomas had a significantly higher Ki-67 index (2.01 ± 3.15%) (Fig. 4) than macroadenomas with or without suprasellar extension (1.12 ± 1.87%). The index was not significantly different in the subgroup of adenomas with invasion of the cavernous sinus compared to groups with other types of invasion.

Studies of our own material concerning the growth rate of inactive adenomas *(3)* revealed a mean labeling index (LI) for MiB-1 of 0.12 (SD 0.29) in adenomas growing less than 1.5 mm and 0.34 (SD 1.05) in adenomas growing more than 1.5 mm per year. For non-invasive adenomas, the MiB-

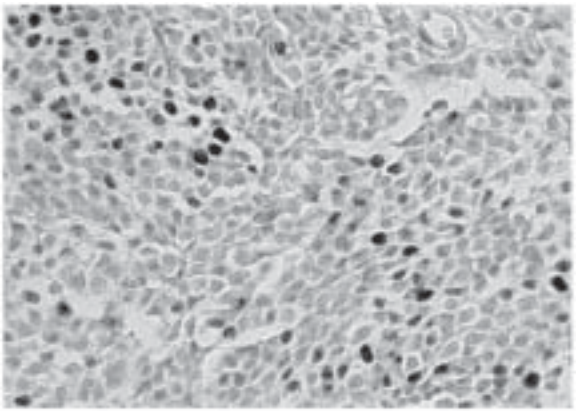

Fig. 5. FSH/LH cell adenoma with many PCNA-positive nuclei. PCNA immunoreaction, ABC, hematoxylin.

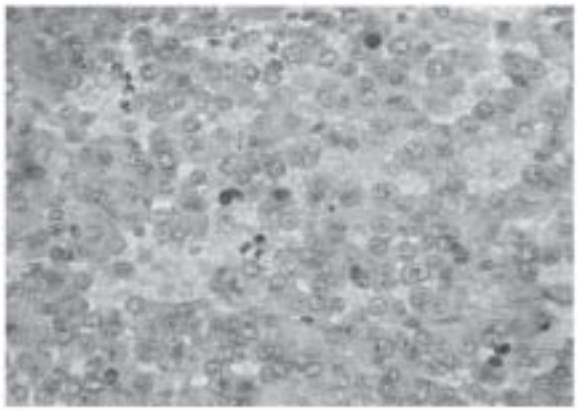

Fig. 6. Oncocytic adenoma with sparse p53-protein-positive nuclei. p53 immuoreaction, ABC, hematoxylin.

1 LI was 0.03 (SD 0.057), for invasive adenomas it was 0.126 (0.273), and for strongly invasive adenomas 0.212 (SD 0.393). The MiB-1 LI was lower in null cell adenomas (LI 0.12, SD 0.25) than in FSH/LH adenomas (0.63, SD 1.28). All these data for MiB-1 were not statistically significantly ($p < 0.005$) different.

In the last WHO classification *(1)*, atypical adenomas are defined by a Ki-67 index of 3% or more clearly showing a poorer prognosis due to decreased operability by more distinct invasiveness, larger size, and accelerated growth.

PCNA

A monoclonal antibody directed against proliferating cell nuclear antigen (PCNA) expressed in late G1 and S phases of the cell cycle was used to investigate whether the proliferative index might help to predict adenoma recurrence *(18)*. This antigen is a nuclear protein identified as the auxiliary protein of deoxyribonucleic acid polymerase delta, and its gene expression correlates with cell proliferation (Fig. 5). Mean percentages of PCNA-positive tumor nuclei in both the initial and the second surgical specimens of the recurrent adenomas were significantly higher than that of the nonrecurrent group *(18)*. Recurrent tumors had a higher PCNA LI than the initial tumors in the same patients. The PCNA nuclear count was not associated with age, sex, or hormone hypersecretion, but was higher in invasive than in enclosed adenomas *(19)*, in macro- than in microadenomas *(18)*, in tumors with extrasellar extension, and in those incompletely excised. A higher PCNA LI also correlated with a shorter disease-free interval *(18)*. Our own studies *(3)* showed that PCNA LI in adenomas growing less than 1.5 mm per year was 0.51 (SD 0.65) in contrast to LI of 1.12 (SD 1.87) for those growing more than 1.5 mm. In non-invasive adenomas the PCNA LI was 0.796 (SD 2.226), in invasive adenomas 0.655 (SD 0.644), and in strongly invasive ones 1.011 (SD 1.241). Null cell adenomas had a lower PCNA LI (0.64, SD 0.85) than FSH/LH cell adenomas (LI 1.57, SD 2.4). We found statistically

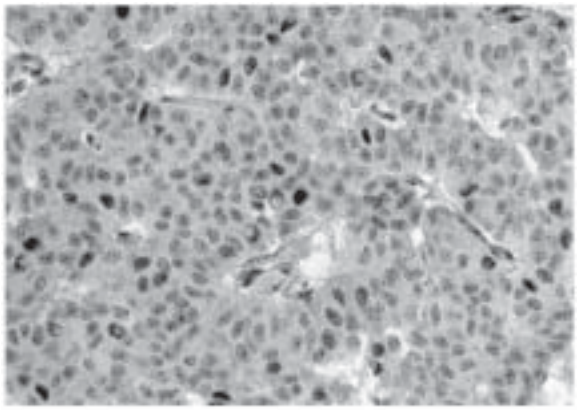

Fig. 7. Null cell adenoma with topoisomerase II a-positive nuclei. Topoisomerase II a immunoreaction, ABC, hematoxylin.

significant differences ($p = 0.037$) for the growth rate und the PCNA expression *(3)*.

p53 Protein

Tumor suppressor gene *p53* mutations have been used in pituitary adenomas to assist in the evaluation of invasiveness and recurrence. Its gene product p53 protein was found to be useful for identification of recurrent pituitary adenomas in childhood and adolescence *(20)*. It correlates with invasive behavior *(21)* and was immunostained in invasive adenomas only *(3)* (Fig. 6). In our studies *(3)* no correlations with the clinical growth rate were found, but p53 expression correlated significantly with numbers of MiB-1–positive nuclei ($p = 0.002$) and PCNA–positive nuclei ($p = 0.0027$).

Topoisomerase IIa

Topoisomerase IIa is demonstrable not in G0 phase but in all other phases of the cell cycle and is the target of several anti-neoplastic agents. In gonadotroph adenomas, null cell adenomas, and ACTH-producing adenomas, the lowest topoisomerase IIa indices are found (Fig. 7), whereas some silent adenomas and pituitary carcinomas have the

highest counts of positive nuclei *(22)*. Although the topoisomerase IIa indices and the Ki-67 indices are similar in most adenoma types, a significant correlation between both is demonstrated only in non-functioning adenomas *(23)*. Topoisomerase IIa is significantly decreased in somatostatin-analog treated GH-producing adenomas compared with untreated tumors. No significant alterations can be found in bromocriptin-treated prolactin-producing adenomas *(22)*.

p27

p27(kip1) (p27) is a member of the universal cyclin-dependent kinase inhibitor (CDKI) family. p27 expression is regulated by cell contact inhibition and by specific growth factors, such as transforming growth factor (TGF)-beta. It is a cell cycle inhibitor by counteracting cyclin E–CDK2 complexes. Its expression is inversely related to Ki-67 *(24,25)*. Forty percent of pituitary adenomas are completely negative, whereas in 33% less than 10% of nuclei are immunostained and in 27% a strong expression is demonstrable *(26)*. In recurrent adenomas p27 shows a lower labeling index (47%) than in non-recurrent adenomas (67%) *(27)*. Vitamin D3 hypophosphorylates p27 and can accumulate p27 protein in pituitary adenomas and was found to arrest the growth of ACTH cells *(28)*.

Hormone Receptors

High concentration of estrogen receptors was observed in tumors derived from cells that are normally the target of this hormone, mainly prolactinomas *(13)*. They were also present in somatotrophic and nonsecreting adenomas, related to the presence of prolactin or gonadotrophin cells in these tumors. They indicate that the tumor cells maintained their differentiation and are correlated with better prognosis especially for prolactinomas *(13)*.

Growth Factors

Many growth factors are expressed in normal pituitary and pituitary adenomas *(29,30)* and some of them have been correlated with increased adenoma progression. Therefore, transforming growth factor-beta (TGF-β) might stimulate prolactin cell adenoma development by inducing tumor cell proliferation and neovascularization by auto- and paracrine mechanisms *(31,32)*. The receptor of the epidermal growth factor is demonstrable in all types of pituitary adenomas and is most abundant in ACTH-secreting adenomas *(33)*, but only in GH secreting adenomas and inactive adenomas its expression correlates with the tumor aggressiveness *(34)*.

The basic fibroblast growth factor (bFGF) together with estrogen induces pituitary transforming gene, and the expression of this pituitary transforming gene coincides with the early lactotrophic hyperplastic response and angiogenesis so that prolactin cell adenoma development may be explained by these mechanisms *(35)*.

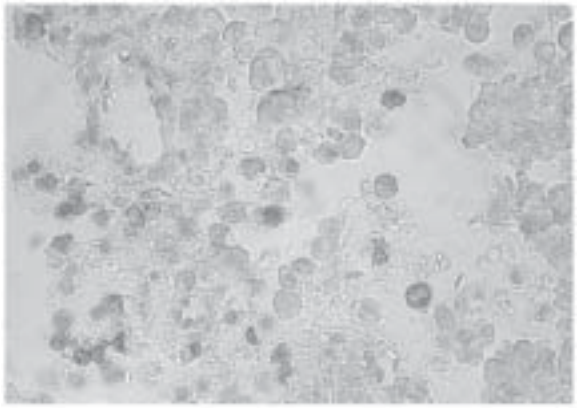

Fig. 8. Sparsely granulated GH cell adenoma with many apoptotic nuclei. TUNEL technique.

The nerve growth factor (NGF) plays a dual role in the pituitary: a local one as a stimulator of differentiation and proliferation of lactotrope cells during pituitary development and a systemic one as a neurohormone that is co-secreted with prolactin into the bloodstream *(36)*. Escape from nerve growth factor control appears to be one of the mechanisms involved in the development and progression of prolactinomas. Exposure of prolactinomas refractory to dopaminergic therapy to exogenous NGF results in their differentiation into lactotrope-like cells reexpressing the D-2 receptor protein. This may open the way to a sequential therapy with nerve growth factor and bromocriptine for patients refractory to the conventional therapy *(36)*.

Our own studies for insulin-like growth factor I (IGF-I) expression *(3)* showed an inverse correlation with age of patients and a higher LI of MiB-1 (1.39, SD 1.82) in IGF-I-negative adenomas than in IGF-I-positive ones (LI 0). Similar data were found for PCNA LI (2.18, SD 2.07, in IGF-I-negative cases; 0.11, SD 0.11, in IGF-I-positive tumors). Nevertheless, there is no evidence that expression of growth factors or their receptors by pituitary tumors can be used for prognosticating the tumor growth.

Apoptoses

Apoptosis (programmed cell death) detected by the *in situ* end-labeling technique was found in 11% of somatotrophinomas (Fig. 8) and 33% of non-functioning adenomas *(37)* and is relatively higher in pituitary carcinomas *(38)*. Correlations between apoptotic rate and prognosis were not reported.

DNA Cytometry

Macroadenomas and invasive adenomas of all subtypes are diploid or non-diploid in similar proportions *(39)* with the exception of prolactin cell adenomas, which show a higher rate of non-diploidy (65%). In comparison to long-term follow-up, neither S-phase fraction nor ploidy corre-

lated with tumor size or invasiveness. Therefore, for long-term follow-up ploidy is an unreliable predictor of tumor persistence or recurrence *(39)*.

Molecular Pathology: Oncogenes and Tumor Suppressor Genes

The expression of the oncogenic form of the epidermal growth factor receptor, c-erbB-2, is not associated with gene amplification or activating mutations to suggest a direct role in pituitary tumorigenesis *(40)* but can be increased in pituitary carcinomas. C-erbB-2 staining was found in the cytoplasm of a variable number of cells in 40% of the invasive adenomas *(19)*, while only 1.2% of the noninvasive tumors expressed this protein *(19)*.

Pituitary oncogenes *gsp*, *ccnd1*, and *PTTG* are abundant in a significant numbers of cases *(41)*. gsp is present in similar to 40% of Caucasian patients with GH-secreting tumors and results from a mutated, constitutively active alpha subunit of Gs protein. Persistent activation of the CAMP–PKA–CREB pathway may lead to uncontrolled cell proliferation and GH secretion. ccnd1 is overexpressed. *PTTG* is expressed in most pituitary tumors. *PTTG* is localized to both the nucleus and cytoplasm and interacts with several protein partners. At least three tumorigenesis mechanisms are proposed for human *PTTG*. (1) *PTTG* and *FGF* form a positive feedback loop and stimulate tumor vascularity. (2) *PTTG* transactivates *c-myc* or other pro-proliferation *genes*. (3) *PTTG* overexpression causes aneuploidy. *PTTG* expression activates p53 and causes p53-dependent and -independent apoptosis.

Cyclins regulate the cell cycle and activate kinases. Cyclin D 1 is sparsely demonstrated and more frequently found in non-functioning and aggressive adenomas than in other adenoma types *(42)*. One study described cyclin D expression in adenomas related to size and tumor regrowth *(43)*. The differences between regrowing and non-regrowing tumors were related to reduced bcl-2 expression, increased cell proliferation, more cells of the G2/M stage, and reduced cell differentiation with more aggressive subsequent behavior. Overexpression of cyclin D3 was found in the nuclei of 68% of inactive adenomas. It correlated to the labeling index of Ki-67 *(43,44)*. Cyclins A, B and E are expressed in all adenoma types and are significantly higher in macroadenomas compared to microadenomas *(43)*.

Somatotroph adenomas can be associated with mutations of the (s) alpha-subunit of G proteins. A better sensitivity of mutated adenomas for somatostatin-analog treatment was shown under in vivo (short- and long-term) and in vitro conditions *(45)*. The percentage inhibition was higher in gsp-positive adenomas and GH hypersecretion was controlled in all patients with gsp mutation even in those in whom tumoral tissue remained after surgery. On the other hand, in the gsp-negative group, somatostain-analog treatment was unable to control hypersecretion in patients bearing tumoral remnants.

Activating mutations of two oncogenes, *GSPT1* and *H-ras*, have also been demonstrated in piutuitary adenomas. In addition, *H-ras* and *c-myc* onogenes but also mutations of the *Rb gene* have been found more often in aggressive tumors. In accordance with this, mutations of the *Rb gene* were shown in pituitary carcinomas. From these findings it can be concluded that amplification of oncogenes (*H-ras* and *c-myc*) and inactivation of tumor suppressor genes (*Rb*, *p53*, *nm23*) play a role in initiation and tumor progression *(16,46)*.

Tumor suppressor genes are *MEN 1 (47,48)*, *RB (49,50)*, *P53* gene *(51)*, *ZAC (52)*, *GADD45 gamma gene (53)*, *p16/CDKN2A (54–58)*, *p 27/KIP 1 (24,59)*. For the *MEN 1* gene found also in some sporadic adenomas, correlations to clinical behavior were not fond.

The allelic loss of an *RB1* intragenic marker on chromosome 13q loss at individual markers is more frequent in invasive adenomas than their noninvasive counterparts *(49, 60)* but did not correlate with immunohistochemical *Rb* detection *(50)*. *p53* gene mutations, at least within the high mutation domains of *p53*, occur infrequently in human pituitary adenomas *(51)*. Increased steady-state levels of p53 protein identified immunohistochemically in some invasive adenomas may therefore be a consequence of binding to other cellular proteins in these tumors. The *ZAC* gene *(52)* encodes a new zinc-finger protein that concomitantly induces apoptosis and cell cycle arrest and localizes to chromosome *6q24-q25*, a well-known hot spot related to cancer. *ZAC* is highly expressed in the adenohypophysis, and its ablation by antisense targeting promotes pituitary cell proliferation. A strong reduction or absence of *ZAC* mRNA and protein expression was detected in nonfunctioning pituitary adenomas, whereas in clinically active pituitary neoplasias, the decrease in *ZAC* expression was variable. Loss of expression was not associated with a mutation of the *ZAC* gene. Correlations to adenoma growth were not evident.

GADD45gamma is a member of a growth arrest and DNA damage-inducible gene family that functions in the negative regulation of cell growth *(53)*. *GADD45gamma* mRNA is found in normal human pituitary tissue, but it is detectable in only few clinically nonfunctioning pituitary tumors by RT-PCR. The gene is not expressed in the majority of GH- or PRL-secreting pituitary adenomas. *GADD45gamma* is a powerful growth suppressor controlling pituitary cell proliferation.

The cyclin-dependent kinase inhibitor 2A/multiple tumor suppressor gene 1 (*CDKN2A/MTS/p16*) plays an important role in the control of progression from G to S phase of the cell cycle through the inhibition of CDK4-mediated RBI phosphorylation. Gene silencing was demonstrated in 78% of nonfunctioning tumors, in contrast to 9.5% of GH secreting adenomas and 0% of histologically normal postmortem pituitaries *(56)*. Results in noninvasive and invasive nonfunctional tumors were approximately equal.

Prognosis After Treatment

Surgical Treatment

Transsphenoidal surgery is the preferred treatment modality for most adenomas (about 90%). Prolactin-producing adenomas are treated by dopamine agonists first. The recurrence rate of pituitary adenomas has been reported to be as high as 10–35% *(18)* or 10–20% *(61)*. The cure rate of adenomas from transcranial surgeries (applied in about 10%) is poorer because only large adenomas growing asymmetrically into suprasellar, retrosellar, or subfrontal regions are resected by this way. Mortality rates are between 0.5% and 1% for transsphenoidal surgeries and between 1% and 2% for transcranial surgeries *(74)*.

According to the therapeutic effectiveness of transsphenoidal microsurgery for pituitary adenomas of all types during the last years, total tumor resection (under microscope) has been achieved in 97.3% of the patients with Hardy *(62)* grade I adenomas (adenomas of less than 10 mm), 95.2% of Hardy grade II (intrasellar adenomas of more than 10 mm), 90.4% of Hardy grade III (locally invasive adenomas), and 47.4% of Hardy grade IV (diffusely invasive adenomas). The percentages of total and subtotal resection achieved extended from 87.6% before 1987 to 96.9% in 2003 *(63)*.

In acromegaly, remission can be achieved in 74% *(64)* of all patients after one operation, including 84% of patients with microadenomas and 64% of patients with macroadenomas. Patients with macroadenomas 11–20 mm in size reached remission in 73%, as compared with a 20% remission rate for patients with adenomas larger than 20 mm. Patients with preoperative growth hormone levels lower than 50 ng/mL had a better outcome (85% remission), whereas growth hormone greater than 50 ng/mL was associated with remission in 30% of the patients *(64)*.

In cases with incomplete tumor removal, radiation therapy may be indicated and in growth hormone–producing adenomas somatostatin analogs can be applied.

In Cushing's disease a primary pituitary surgery leads to a constant remission in 73.5% *(65)*. If the disease persists or recurs, treatment options including second-look surgery, bilateral adrenalectomy, medical treatment or radiotherapy should be considered.

Medical Treatment

Medical therapy is indicated as initial treatment for most patients with prolactin-producing adenomas and some patients with growth hormone–secreting tumors.

In prolactin-producing tumors treatment with dopamine agonists reduces prolactin levels in about 90% of patients *(66)*. The decrease of prolactin is accompanied by a significant shrinkage of the tumor volume by at least 25% in 79% of cases; 89% shrink to some degree. Most shrinkage occurs during the first 3 mo of treatment *(67)*. The histological basis of this often very impressive reduction of adenoma volume is a strong shrinkage of the single adenoma cells *(68,69)*. About 10% of patients treated with dopamine agonists first have to be operated due to non-response or non-tolerance of dopamine agonists *(66)*.

In acromegaly somatostatin analogs, dopamine agonists, and growth hormone antagonists can be used. By interacting with somatostatin receptors, somatostatin analogs inhibit hormone secretion from the tumor with normalizing of IGF-I in 66% of patients *(70)* and induce tumor shrinkage in half of patients *(71)*.

TSH-secreting adenomas may also be treated with somatostatin analogs. A normalization of of TSH could be achieved in 95% and a tumor shrinkage in 52% of patients *(72)*.

Drugs such as dopamine agonists and cyproheptadine are inappropriate to reduce ACTH secretion in Cushing's disease. Adrenal steroid hormone production can be reduced by ketokonazole, mitotane, and metyrapone, but surgery remains the most effective treatment *(73)*. Clinically inactive adenomas react only rarely on dopamine agonists, somatostatin analogs, or antagonists *(74)*.

Radiation Therapy

Postoperative radiation therapy for pituitary adenomas is usually reserved for extensive lesions or for those that are incompletely resected. In a study of 19 patients *(75)* who underwent external beam irradiation for salvage, two patients have died of progressive adenoma, two are alive with disease progression, eight were alive without disease progression, and seven have died of intercurrent disease within a median follow-up time of 11.8 yr from the time of surgical failure. The 5-, 10-, 15-, and 20-yr overall actuarial (and progression-free) survival rates were 79% (90%), 62% (90%), 44% (80%), and 44% (53%), respectively. Dose of radiation, suprasellar extension at the time of surgical failure, and histologic findings had no bearing on prognosis in this study *(75)*.

Radiotherapy is used for treatment of patients with incompletely excised or recurrent tumors or for endocrine-active tumors that cannot be controlled by other therapy *(76,77)*. Gamma knife stereotactic radiosurgery has a more rapid and stronger effect than the fractionated radiotherapy and can be used for small enclosed adenomas in inoperable patients *(78,79)*.

In a study *(80)* of 47 patients first operated and successively conventionally irradiated, patients with acromegaly (40 with persistent, 7 with recurrent disease) the 5-, 10- and 15-yr overall survival rates were 98%, 95%, and 93%, respectively. Suppression of GH during oral glucose tolerance test was seen in 9% of patients at 2 yr, 29% at 5 yr, 52% at 10 yr, and 77% at 15 yr. Local tumor control was 95% at 5, 10, and 15 yr after treatment. Late toxicity was mainly represented by progressive hypopituitarism, which was present in 33% of patients at baseline and increased to 57%, 78%, and 85% of patients at 5, 10, and 15 yr after radiotherapy.

For patients with irradiated pituitary adenomas, the cumulative risk of second brain tumors was found *(81)* to be

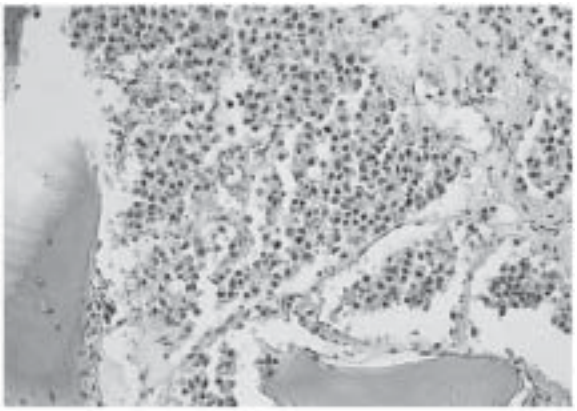

Fig. 9. Bone metastasis of prolactin-cell carcinoma. Hematoxylin–eosin.

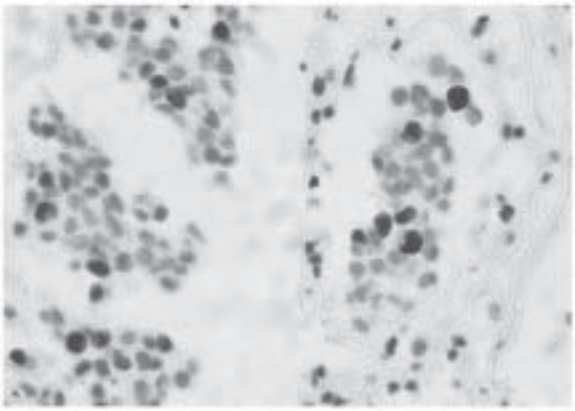

Fig. 10. GH cell carcinoma with many MiB-1–positive nuclei. MiB-1 immunoreaction, ABC, hematoxlin.

2.0% [95% confidence interval (CI), 0.9–4.4%] at 10 yr and 2.4% (95% CI, 1.2–5.0%) at 20 yr, measured from the date of radiotherapy. The relative risk of second brain tumor compared with the incidence in the normal population is 10.5 (95% CI, 4.3–16.7). The relative risk is 7.0 for neuroepithelial and 24.3 for meningeal tumors. The relative risks are 24.2 (95% CI, 4.8–43.5), 2.9 (95% CI, 0–8.5), and 28.6 (95% CI, 0.6–56.6) during the intervals 5–9, 10–19, and more than 20 yr after radiotherapy. There is no evidence of excess risk of second systemic malignancy *(81)*.

As a late effect of radiotherapy, several cases of osteosarcoma or fibrosarcoma developing from 4 to 21 yr after irradiation for pituitary adenomas or craniopharyngiomas were reported *(10,82–84)*.

Pituitary Carcinomas

Most pituitary carcinomas develop from invasive relapsing adenomas. The tumor, its connective tissue, and its surrounding structures may be altered by one or more foregoing surgeries and/or radiation therapies in a way that enables tumor cells to invade vessels for metastatic spread (Fig. 9).

Pituitary carcinomas are very rare neoplasms (about 100 tumors published up to now). Most were ACTH-secreting or prolactin secreting tumors. GH-positive *(85)* or inactive tumors develop very rarely into carcinomas *(86)*. Pituitary carcinomas show a higher index of Ki-67 (Fig. 10) and p53 protein and a lower expression of p27 *(87)* in the primary tumor and in metastases. Ras mutations can be found in prolactin cell carcinomas *(88)*. Increased PCNA index and c-erbB-2 membrane staining were demonstrated in sellar tumor and its metastasis *(19)*.

The prognosis of pituitary carcinomas is generally poor, although patients with long-term survival are described *(89)*. Owing to the small number of cases, collections large enough for correlations between different strategies of therapy and prognosis do not exist.

Conclusions

The prognosis of pituitary adenomas depends mainly on its operability in the first or second surgery. If it can be totally resected, there are no differences between invasive and enclosed adenomas and between larger and smaller adenomas. We do not know up to now whether the same is also true for atypical adenomas.

Furthermore, if adenomas were treated with drugs (especially dopamine agonists or somatostatin analogs), the reactions (decrease of elevated hormones, shrinkage of tumor volume) are most important for prognosis. If the effect is insufficient, the prognosis depends on the results of the following surgery.

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