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Abstracts

WHAT IS NEW IN THE DIAGNOSTICS AND TREATMENT OF THE NERVOUS SYSTEM TUMOURS?

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ORGANIZERS

The Team of Oncologic Neuropathology of the Committee of Neurological Sciences, Polish Academy of Sciences

Department of Experimental and Clinical Neuropathology,
Mossakowski Medical Research Centre, Polish Academy of Sciences

Department of Medical Pathomorphology, Medical University of Bialystok

Foundation of the Medical University of Białystok

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A case of anaplastic ganglioglioma in adolescent patient with epilepsy

Maciej Ciołkowski[1,3], Paweł Kowalczyk[1], Paweł Daszkiewicz[1], Dagmara Szymkowicz[1], Wojciech Nowak[1], Marcin Roszkowski[1], Wiesława Grajkowska[2,4]

[1]Department of Neurosurgery, Children's Memorial Health Institute, Warsaw
[2]Department of Pathology, Children's Memorial Health Institute, Warsaw
[3]Department of Descriptive and Clinical Anatomy, Medical University of Warsaw
[4]Department of Experimental and Clinical Neuropathology, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw

16 years old male with eight years history of epilepsy and conduct disorder was admitted for planned surgical treatment. MRI revealed a contrast enhancing focus located in the temporal pole of the right cerebral hemisphere surrounded by region of hyperintensive signal in FLAIR images, which involved the medial temporal structures. The temporal topectomy and amygdalo-hippocampectomy was performed.

The histopathological study of the tumour showed relativly numerous dysplastic ganglion cells within astrocytic glial component of pleomorphic cells, with increased number of pathological mitotic figures and microvascular proliferation. The immunohistochemical studies confirmed diagnosis of anaplastic ganglioglioma. The surrounding cortex showed features of laminar disarrangement consistent with diagnosis of focal cortical dysplasia, type IIIb.

However the gangliogliomas are the most common tumours associated with temporal lobe epilepsy, the anaplastic glial element in these neoplasms is a rare finding, in particular in paediatric population.

Awake brain surgery in adult patients

Tomasz Dziedzic[1], Marek Prokopienko[1], Aleksandra Bala[1,2], Anna Podgórska[1], Jolanta Piwowarska[3], Andrzej Marchel[1]

[1]Department of Neurosurgery, Medical University of Warsaw
[2]Faculty of Psychology, University of Warsaw
[3]II Department of Anesthesiology and Intensive Care, Medical University of Warsaw

Awake craniotomy is performed as the standard surgical approach to supratentorial intraaxial tumors, located within proximity of eloquent cortex areas (language, vision, movement, etc.) and subcortical white matter tracts. We present the protocol for awake brain tumour surgery used in the Department of Neurosurgery of Medical University of Warsaw. We share our indications/contraindications for this kind of procedure, neuroradiological imaging protocol, neuropsychological testing techniques, anaesthesiological protocol, neurophysiological protocol, surgical technique and prospectively collected data about 11 patients surgically treated by the same operative team at a single institution. The group included five women and six men, in the mean age of fifty-five years old (range: 20-70 years old).

Mandatory neuroradiological studies include not only standard sequences for magnetic resonance imaging, but also functional imaging studies (fMRI) and tractography (DTI) – with special attention to corticospinal tracts, language related tracts and visual pathway. Preoperative psychological examination of awake surgery candidates includes evaluation of stress coping strategies, emotional stability, as well as neuropsychological assessment of presence and level of language deficits and general cognitive status. Before the surgery neuropsychologist and a patient choose and practice all tasks that will be useful and used during the procedure. These tasks include: naming the pictures, reading, calculating and finally simple motion sequences. All procedures were performed according to an awake-awake-awake protocol. Anatomical tumour's margins were defined by magnetic resonance based image guidance. Before corticotomy, cortical mapping and functional borders of the tumour were identified. Standard microsurgical technique was used for tumour removal, including subcortical dissection. During white matter dissection safe margins of the resection were defined by subcortical mapping. Patient presentations, comorbid conditions, tumour locations, and the histological characteristics of lesions were recorded. Brain mapping was possible in all 11 patients. All patients had tumours in the proximity to language cortices – in 7 cases near the Wernicke's area and the rest close to the Broca's area. Most (seven) patients were operated due to high-grade glioma, three of them due to low-grade glioma and one patient due to metastatic brain tumour. In postoperative period in 5 cases we observed new neurological deficits, but these were permanent only in one case. Complication rates were higher in patients with high-grade gliomas and preoperative neurological deficits. None of neurologically intact patients presented a permanent neurological deficit postoperatively.

Awake craniotomy is an effective surgical approach to supratentorial tumours located within eloquent cortex with a low complication rate. It should be the standard surgical treatment if tumour is within cortical language sites or subcortical language pathways. This technique is

the only one which gives the opportunity for cortical and subcortical mapping of language functions.

Subventricular zone involvement determines the efficacy of salvage radiosurgery for recurrent glioblastoma

Sebastian Dzierzęcki[1,2], Marek Harat[2,3], Katarzyna Dyttus-Cebulok[2,4], Mirosław Ząbek[1,2]

[1]Department of Neurosurgery, Postgraduate Medical Center, Warsaw
[2]Gamma Knife Centre, Warsaw
[3]Department of Oncology and Brachytherapy , Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, Torun
[4]Teleradiotherapy Department, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw

The main aim of this study was to determine the efficacy of stereotactic Gamma Knife radiosurgery (SRS) as a salvage treatment in patients with recurrent glioblastomas as well as to determine whether subventricular zone involvement (SVZ) was a prognostic marker for positive outcomes of gamma knife radiosurgery (GKS) for recurrent glioblastoma (GBM).

Between July 2012 and December 2016, 19 consecutive patients with 23 lesions were treated with SRS gamma knife as salvage treatment for recurrent glioblastoma.

The primary end point was overall survival duration from the time of the actual salvage radiosurgery.

All available MR images were reviewed to identify areas of new or progressive enhancement in relation to the patients' previous treatment.

All patients were initially placed in a stereotactic head frame, followed by contrast-enhanced magnetic resonance imaging (MRI) for treatment planning. A neurosurgeon and a radiation oncologist were involved in treatment planning and target volume determinations for all 19 patients. The median tumor volume was 4.39 cm^3 (range, 0.09-12.25 cm^3). The median marginal dose of 18 Gy (range, 15-20 Gy) was always given to the 50% isodose line.

All patients included in this study received a standard course of radiotherapy after surgical resection or biopsy with a median dose of 54 grays (Gy) (range, 42-60 Gy) in conventional fractionations of 2 Gy per day. After radiotherapy, 14 patients had subsequently received temozolomide. The mean time from the initial diagnosis to salvage radiosurgery was 15.6 months (range, 1-66 months).

An actuarial survival analysis for the all patients revealed a median overall survival duration of 32.2 months after the initial diagnosis (95% CI 24.8-39.5 months) and 16.6 months after the date of SRS (95% CI 12.5-20.6 months). The median survival time after salvage SRS was significantly higher in patient presenting no SVZ engulf at time of Gamma Knife irradiation comparing with patient showing SVZ infiltration and both SVZ and cortical involvement (20.6 months vs 8 months vs 15 months, p = .019). In conclusion our analysis supports that SRS Gamma Knife is a safe and effective salvage modality in selected patients with recurrent glioblastomas. Additionally, obtained results suggest that involvement of SVZ could be used as independent poor prognostic factor thus targeting regions with SVZ involvement might serve as new promising strategy for prolonging overall survival in glioblastoma patients.

Paediatric brain tumours. The 2016 WHO Classification of Tumours of the Central Nervous System

Wieslawa Grajkowska

Department of Pathology, The Children's Memorial Health Institute, Warsaw
Department of Experimental and Clinical Neuropathology, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw

The 2016 CNS WHO classification includes both histopathological and molecular parameters for improvement diagnosis of brain tumours. The major changes concern diffuse gliomas, medulloblastomas and other embryonal tumours, and include new entities which are defined by molecular markers. The paediatric gliomas with a diffuse growth pattern in the midline location especially diffuse intrinsic pontine glioma (DIPG) with driver mutations in histone genes *H3F3A* and rarely *HIST1H3B*; were defined as diffuse midline glioma, H3 K27M-mutant. All of them are associated with poor prognosis. The new entity is also RELA fusion-positive ependymoma. This type of ependymoma occurs mainly in children in supratentorial location. L1CAM expression may be a potential immunohistochemical surrogate marker for diagnostic test of this tumour. Recently diagnosis of meduloblastoma requires histological and molecular classification. Parallel to histological variants of medulloblastoma: classic, desmoplastic/nodular, medulloblastoma with extensive nodularity, large cell/anaplastic, four molecular groups: WNT-activated, SHH-activated, group 3, and group 4 are distinguished. Additionally, in SHH-activated meduloblastoma *TP53* gene status is very important. Medulloblastoma SHH-activated subgroup is divided into two subgroups: SHH-activated *TP53*-

wild type or *TP53*-mutant. Moreover the presence of *TP53* mutation is associated with poor prognosis.

Another group of paediatric brain tumours which have undergone changes in their classification are embryonal tumors. The 2016 CNS WHO classification excluded the term primitive neuroectodermal tumor (PNET). The new entity with amplification of the C19MC region on chromosome 19 was included. The presence of C19MC amplification results in a diagnosis of embryonal tumor with multilayered rosettes (ETMR), C19MC-altered. In the absence of C19MC amplification, a tumor with histological features ETMR ought to be diagnosed as embryonal tumor with multilayered rosettes, NOS but other tumours with histological features of medulloepithelioma should be diagnosed as medulloepithelioma, as previously.

Atypical teratoid/rhabdoid tumor (AT/RT) is now defined by alterations of either *INI1* or *BRG1* gene. The cases with histological features of AT/RT without of characteristic, diagnostic alterations, should be diagnosed as CNS embryonal tumours with rhabdoid features. Tumours previously designated as CNS PNET without diagnostic molecular alterations are described as CNS embryonal tumour, NOS. Nowadays proper diagnosis of pediatric brain tumors requires inclusion of molecular markers in routine practice.

Immunohistochemical diagnostics of brain tumors

Ewa Iżycka-Świeszewska

Department of Pathology and Neuropathology, Medical University of Gdansk
Pathomorphology Department, Copernicus Hospital, Gdansk

Immunohistochemistry (IHC) is an important element of a modern approach to brain tumor diagnostic. IHC results always need a correlation with tumor morphology, taking in consideration neoplastic tissue heterogeneity. Antibody panels, not single antibodies should be routinely used in diagnostic neuro-oncology practice. Several important antibodies have been recently introduced and have pivotal impact on the diagnosis accuracy in glial tumors. IHC surrogates for molecular markers such as anty-IDH1 R132, ATRX, PTEN, hTERT, BRAF V600 play increasing role in primary tumors. Many diagnostic and predictive markers are in use in metastases to the brain. The quality control in neuropathological immunohistochemistry is necessary to minimize the interpretation pitfalls. IHC serves a potential tool for personalized treatment of brain tumors.

Unusual meningeal sarcoma with extraordinary molecular features

Ewa Izycka-Swieszewska[1], Markku Martti Miettinen[2], Jerzy Lasota[2], Wojciech Kloc[3], Piotr Lass[4], Edyta Szurowska[5], Blanka Hermann-Okoniewska[1]

[1]Department of Pathology and Neuropathology, Medical University of Gdansk; Pathomorphology Department, Copernicus Hospital, Gdansk, Poland
[2]Laboratory of Pathology, National Cancer Institute, Bethesda, MD, USA
[3]Neurosurgery Department, Copernicus Hospital, Gdansk; Department Of Neurosurgery UWM, Olsztyn, Poland
[4]Department of Nuclear Medicine and Radiology Informatics, Medical University of Gdansk, Poland
[5]2nd Department of Radiology, Medical University of Gdansk, Poland

Sclerosing epithelioid fibrosarcoma is a rare neoplasm typically presenting as a soft tissue mass in the middle-aged adults. It gives local recurrences and late metastases. The characteristic recurrent molecular finding is *EWS-CREB3L* fusions.

Here we present an extremely rare case of a primary sclerosing epithelioid fibrosarcoma of dura mater with exceptional molecular aberration *EWSR1-ATF1* fusion.

It was a 1.5 cm nodule with a radiological features of metastatic lesion. Histologically the tumor was composed of uniform proliferation of epithelioid cells, with vesicular nuclei, arranged in cords within a sclerotic collagenous matrix with focal necroses. Focal cerebral invasion was present, and proliferation index Ki67 up to 10%. Immunophenotyping revealed expression of vimentin, MUC4, desmin, Glut1, collagen4, and CD99, and additionally in part of the cells CD56, NSE, EMA and synaptophysin positivity. The final diagnosis was established in a consultation referential center.

Sclerosing epithelioid fibrosarcoma should be included in a differential diagnosis of dural tumors.

Analysis of DNA methylation in non-functioning pituitary adenomas – an attempt to identify invasiveness-related abnormalities

Paulina Kober[1], Joanna Zbijewska[1,2,3], Nataliia Rusetska[1], Maria Maksymowicz[4], Krzysztof Goryca[5], Jacek Kunicki[6], Wiesław Bonicki[6], Janusz A. Siedlecki[1], Mateusz Bujko[1]

[1]Department of Molecular and Translational Oncology, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw

[2]Faculty of Chemistry, Warsaw University of Technology, Warsaw
[3]Faculty of Mathematics, Informatics and Mechanics, University of Warsaw, Warsaw
[4]Department of Pathology, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw
[5]Department of Genetics, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw
[6]Department of Neurosurgery, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw

Clinically nonfunctioning pituitary adenomas (NFPAs) are common intracranial tumors. They are considered as benign neoplasms, however notable proportion of these tumors exhibit invasive growth, that hinders complete surgical resection and results in higher risk of recurrence. Potentially, biomarkers of invasiveness could be useful for patient management. We looked for epigenetic abnormalities in NFPA samples to verify whether impaired DNA methylation may play a role in development of invasive phenotype.

HumanMethylation450K (Illumina) microarrays were used to profile DNA methylation in a group of 34 NFPA patients as well as control samples from normal pituitary. DNA methylation level of selected genomic loci was assessed in a group of 75 NFPAs with bisulfite pyrosequencing, whereas the expression level of corresponding genes was evaluated with qRT-PCR.

NFPAs exhibited distinct global DNA methylation profile and higher overall methylation level as compared to normal pituitary. However, only slight, statistically insignificant, differences of global methylation DNA level were observed between invasive (n = 18) and noninvasive (n = 16) tumors. Accordingly, we didn't identify significantly differentially methylated particular genomic positions, when using straight statistic criteria.

The analysis of promoter regions of *ITPKB* and *CNKSR1* genes, identified as probably differentially methylated in invasive and atypical NFPAs, respectively, revealed significant difference in DNA methylation in NFPAs stratified according invasiveness status. The expression of *ITPKB* and *CNKSR1*was inversely correlated with promoter methylation level.

The results indicate very similar DNA methylation profile of invasive and noninvasive NFPAs. Differentially methylated genomic regions can be found, including promoter of *ITPKB* and *CNKSR1*, however DNA methylation testing doesn't seem to be useful as indicator of tumor invasiveness.

Impact of advanced intraoperative monitoring on outcome of brain tumor resection in eloquent areas

Witold Libionka[1,2], Piotr Murawski[1], Jakub Wiśniewski[1,3], Patryk Kurlandt[1], Maciej Racinowski[1], Stanisław Adamski[1], Ewa Szutowicz[4], Ewa Iżycka-Świeszewska[5,6], Blanka Hermann[5,6], Katarzyna Czarnota[5,6], Karolina Gizelbach-Żochowska[5], Wojciech Kloc[1,7]

[1]Department of Neurosurgery, Copernicus Hospitals, Gdańsk
[2]Chair of Rehabilitation and Kinesiology, Gdansk University of Physical Education, Gdańsk
[3]Department of Surgery and Urology for Children and Adolescents, Medical University of Gdansk, Gdańsk
[4]Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdańsk
[5]Department of Pathology and Neuropathology, Medical University of Gdansk, Gdańsk
[6]Department of Pathomorphology, Copernicus Hospitals, Gdańsk
[7]Department of Neurology and Neurosurgery, University of Warmia and Mazury, Olsztyn

Aim: Assessment of impact of neuronavigation-merged fiber tracking, intraoperative neuromonitoring and intraoperative speech evaluation on safety and extent of tumor resection in eloquent brain regions.

Material and methods: Medical records of 45 patients who underwent resection of tumors in eloquent brain regions between 2013 and 2017 were reviewed. Based on 1.5 MRI neuronavigation-merged fiber tracking visualized pyramidal tract in all patients, arcuate fasciculus-additionally in 7 patients, and optic radiation – in 3 patients. Distance between tumor and pyramidal tract varied between 0 and 15 mm; between the lesion and arcuate fasciculus – between 2 and 12 mm; and between the lesion and optic radiation – between 2 and 5 mm. In 18 cases cortical and subcortical electrophysiological mapping was performed, in 2 cases monitoring of visual evoked potentials, and in 5 – awake surgery to monitor speech. Control CT/MR were obtained 1 day, 3 and 6 months after surgery.

Results: Among 45 patients, gross total resection (> 95%) was achieved in 36 (82.2%), and subtotal (> 80%) in 8 (17.8%) patients. Postoperatively 6 (13.3%) patients displayed neurological deficits. On 6-month follow-up none of them presented pyramidal signs, 2 (4.4%) displayed mild aphasia. Neuropathologic examination revealed glioblastoma multiforme in 25 cases, anaplasic astrocytoma in 3 cases, anaplastic ganglioglioma in 1 case, anaplastic neurocytoma in 1 case, diffuse astrocytoma in 3 cases, oligodendroglioma/oligoastrocytoma in 6 cases, and metastatic tumors in the remaining 6 cases.

Conclusions: Neuronavigation-merged fiber tracking combined with intraoperative neuromonitoring is a useful

tool in surgery of tumors in eloquent brain areas ensuring low risk of permanent neurologic deficits and satisfactory completeness of resection. Both methods are complementary and should be used in parallel.

Is there still a place for electron microscopy in the diagnosis of brain tumours

Pawel P. Liberski

Department of Molecular Pathology and Neuropathology, Medical University of Lodz

Electron Microscopy (EM) – "the Big Eye of the XX century". EM is a technique no longer widely used in the field of surgical neuropathology of brain tumours, as it has been replaced by immunohistochemistry with ever-growing number of more or less specific antibodies commercially available. However, it is still a powerful technique if diligently used, especially if applied to a small brain tumour biopsy specimens. In this lecture, I will systematically review ultrastructural findings in the numerous of categories of brain tumours. Over the last quarter of century, I have studied a large collection of brain tumour specimens immediately fixed for electron microscopy at the neurosurgical theatre. **Fibrillary astrocytomas** consisted of a mixture of cell bodies and their processes. The cytoplasm contains innumerable glial intermediate filaments. **Gemistocytic** cells contain slightly more indented peripherally located nuclei while the whole cytoplasm is densely filled with glial filaments with some subcellular organelles in the centre. **Pilocytic astrocytomas** are typically biphasic tumors in which stellate, fibrillar areas, which also show microcystic degeneration, are intermingled with more solid parts, composed of bipolar elongated "pliocytic" cell. Two types of distinctive structures are relatively common in pilocytic astrocytomas: "*eosinophilic hyaline droplets*" (EHDs) and "*round granular bodies*". Electron microscopy of **pleomorphic xanthoastrocytoma (PXA)** reveals innumerable astrocytes frequently connected by plaque-like long junctions or hemidesmosomes, which intermingle with dense bundles of collagen fibers. Numerous Rosenthal fibres of different **shapes** and in different stages of development may be observed. The majority of the astrocytic tumour cells are covered with basal laminae. **Subependymal giant cell astrocytoma** consists of large gemistocyte-like cells and giant, bizarre globoid cells with eosinophilic cytoplasm and peripherally located vesicular nuclei which contain a prominent nucleolus. Ultrastructurally, these giant cells contain innumerable glial filaments, numerous ribosomes, distended endoplasmic reticulum, electron-dense bodies and peculiar crystalloids. The latter are needle-like, rectangular or rhomboid. **Oligodendrogliomas** are rather monotonous tumours with round and oval nuclei without indentations and cytoplasm of an electron-density lower than that of astrocytic tumours, Probably the most characteristic, but not entirely specific, features of oligodendrogliomas are concentric arrays of membranes (so called membrane laminations, whorls or scrolls). The ultrastructural pattern of **ependymomas** is florid and characteristic with a picture dominated by the presence of microlumina, cilia with basal bodies (blepharoplasts), microvilli and long, interdigitating intercellular "zipper-like" junctions of the *zonulae adherentes* (adhesive plaque junctions) type. In **gangliogliomas** the majority of the neoplastic neurons are large, polygonal or oval with well-developed subcellular organelles, round nuclei and prominent nucleoli. An abundance of dense core vesicles is seen in both the tumor cell bodies as well as in processes. The most intriguing ultrastructural finding of gangliogliomas is abundant autophagic vacuoles. These vesicular structures are observed in neuronal perikarya, synaptic terminals and in dystrophic neurites. The autophagic vacuoles are of different size, mostly double membrane bound. Some of them contain cellular organelles (mainly mitochondria) some parts of cytoplasm and amorphous usually electron-dense material. It is widely believed that autophagy may lead to cell death, termed programmed cell death type II. The process of macroautophagy is initiated by formation of a double membrane bound vacuole, termed the autophagosome which later fuses with a lysosome to create autophagolysosome. **Central neurocytoma** is characterized by typical rounded neuronal cells containing dense-cored vesicles, analogous to those described in gangliogliomas. The major component of **medulloblastoma** is densely packed cells with scanty electron-dense cytoplasm and sparse but otherwise typical organelles. Some nuclei were extremly invaginated; intranuclear pseudoinclusions and nuclear bodies were infrequently observed. Neurite-like processes which contained abundant parallel microtubules were frequent and could be occassionally traced to a cell body. Such "neuritis" occasionally formed highly branched structures and were virtually identical with embryonal neurites or growing cones. Pleomorphic dense-cored vesicles, neurotubules, synaptic terminals and specializations, and intercellular adhesion plaque junctions were rarely observed. Interestingly, junctions which connected cellular processes with dense-core vesicles and the cytoplasm of neoplastic cells were occasionally seen. The latter phenomenon suggests formation of abortive synaptic ribbons.

Molecular stratification of selected childhood brain tumours

Maria Łastowska

Department of Pathology and Clinic of Oncology,
The Children's Memorial Health Institute
Department of Experimental and Clinical Pathology,
Mossakowski Medical Research Centre Polish Academy
of Sciences, Warsaw

Prognostic stratification of childhood brain tumours, based on existing clinical and histopathological criteria, is not adequate for a number of patients who were ascribed to particular risk groups. Meanwhile, integrated use of technologies for whole genome analysis revealed molecular heterogeneity of all analysed so far high grade brain tumours. Moreover, the molecular groups correlate with histological types and clinical features, including survival of patients. Taking into account these discoveries, recent 4th revision of WHO Classification of Tumours of the Central Nervous System (WHO 2016) introduced molecular findings to the current classification of brain tumours.

For molecular characterisation of tumours it is particularly important that the employed methods allow for analysis of Formalin-Fixed Paraffin-Embedded (FFPE) tissues.

Recently, the nCounter Gene Expression Assay (NanoString) has been introduced which provides a method for direct detection of mRNAs without the use of amplification or reverse transcription, the steps essential in analysis of microarrays or Real-Time PCR. In consequence, it is possible to analyse degraded RNA for reliable assessment of genes expression levels.

Retrospective analysis of medulloblastoma, the most common malignant brain tumour in children, based on NanoString method, allowed for identification of four molecular groups of this disease: Wingless (WNT), Sonic Hedgehog (SHH), Group 3 and Group 4 tumours. The molecular groups correlated with histological types (e.g. SHH tumours with desmoplastic/nodular variant), clinical features (e.g. rare metastases in WNT tumours) and especially with survival of patients. Remarkably, patients with WNT tumours have a favourable outcome and a reduction of the radiation dose is being considered for those patients.

Another method based on analysis of FFPE material using methylation profiling of tumours allowed for discovery of four new tumour entities displaying a unique methylation profiles, which were previously classified as CNS-PNETs. They are named after the presence of specific genetic rearrangements as "CNS NB-FOXR2", "CNS EFT-CIC", "CNS HGNET-MN1" and "CNS HGNET-BCOR". Importantly, these tumours are characterised by different clinical features, e.g. "CNS HGNET-MN1" tumours are associated with better survival rates as opposite to "CNS HGNET-BCOR" tumours.

In light of the above findings, biological characterisation of childhood brain tumours is essential if we are to improve diagnosis and treatment of patients.

Granular cell tumor – a rare neoplasm of the neurohypophysis and suprasellar region: clinicopathological and ultrastructural study of 5 cases

Maria Maksymowicz[1], Grzegorz Zieliński[2], Jacek Kunicki[3], Monika Pękul[1], Agata Piaścik[1], Andrzej Styk[2], Ewa Matyja[4], Wiesława Grajkowska[5], Wiesław Bonicki[3]

[1]Department of Pathology and Laboratory Diagnostics, Maria Sklodowska-Curie Institute – Oncology Center, Warsaw
[2]Department of Neurosurgery, Military Institute of Medicine, Warsaw
[3]Department of Neurosurgery, Maria Sklodowska-Curie Institute – Oncology Center, Warsaw
[4]Department of Clinical and Experimental Neuropathology, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw
[5]Department of Pathology, The Children's Memorial Health Institute, Warsaw

Introduction: Granular cell tumors (GCTs) are rare, poorly understood sellar region lesions, arising in the neurohypophysis and/or pituitary stalk. There have been less than 90 cases of GCT reported in the literature. The 2016 WHO Classification of Tumors of the Central Nervous System and the 2017 WHO Classification of Endocrine Tumors defines these entities as the *TTF-1-positive GCTs of the neurohypophysis*. It is believed that they might derived from the granular pituicytes of the posterior pituitary gland. They are nonfunctioning, benign tumors (WHO grade I). Majority of the GCTs occur in the fourth or fifth decade of life with a slight female predominance. Radiological findings consist of large, solid tumors with suprasellar extension. Preoperative distinguishing from other sellar tumors is not possible. Clinical manifestations of the GCTs are tumor mass compression, visual disturbances, headaches, hypopituitarism or hyperprolactinemia. The total resection is the treatment of choice. The tumors tend to be firmer than the pituitary adenomas and they have high tendency for bleeding during surgery. Histologically, GCTs are composed of polygonal cells with granular cytoplasm. These tumors show nuclear immunoreactivity for TTF-1 (thyroid transcription factor 1).

Aim: To report a five cases of surgically resected GCTs between 2000 and 2017 in the Oncology Center and Military Institute of Medicine.

Material and methods: Among more than 4500 sellar tumors, GCT was diagnosed in five patients (four women and one man); the mean age of patients was 45 years (range 26-57 years). All patients underwent preoperative and postoperative MRI examination; all cases were radiologically and clinically indistinguishable from nonfunctioning pituitary adenomas. Patients were operated on by three neurosurgeons in the two clinics. All cases were histopathologically and ultrastructurally diagnosed.

Results: At preoperative MRI, 3 tumors were suprasellar, 1 was combined intra- and suprasellar, and 1 was intrasellar. Main presenting symptoms were visual impairment (3/5 cases) and hypogonadism (4/5 cases); all tumors were nonfunctioning. All cases were effectively treated by simple excision (3 patients were operated through a transsphenoidal approach and 2 – transcranial); in 1 case resection was subtotal, but without recurrence. After operation 4 patients developed diabetes insipidus. In all cases improvement was achieved and patients were still stable on the last date of follow-up (range 4 to 9 years). In all cases tumor cells were large, oval or polygonal, with abundant, granular and eosinophilic cytoplasm. All tumors showed nuclear immunoreactivity for TTF-1 and diffuse immunopositivity for S100 protein, vimentin and galectin-3. Stains for GFAP, pituitary hormones, cytokeratin and chromogranin A were negative. The Ki-67 (MIB-1) proliferative index was uniformly low, ranging from 1% to 5%. At electron microscopy level, GCTs were composed of densely packed neoplastic cells with small desmosomes and a high content of electron-dense lysosomes. No secretory granules were identified.

Conclusions: Because of similarities on MRI to other much more common lesions as pituitary adenomas, the preoperative diagnosis of GCT is not possible. GCTs are firm, very vascular and prone to heavy bleeding during surgical resection; radical resection is difficult or not possible. Most GCTs are entirely suprasellar or mixed supra- and intrasellar in location; they often occure with visual and endocrinological disturbances. Immunohistochemical and ultrastructural diagnosis is necessary to recognize GCT and its optimal management.

Tumours of the central nervous system according to the new WHO 2016 classification

Ewa Matyja

Department of Experimental and Clinical Neuropathology, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw
Department of Neurosurgery, M. Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw

The 2016 WHO Classification of Tumors of the Central Nervous System, which is in fact a revised 4th edition, for the first time incorporates genetic characterization to identify many tumour entities. Molecular alterations appear to be of great prognostic value especially in gliomas and embryonal tumours. The proposed so-called "integrated diagnosis", based on 4-layered reporting format, includes conventional histological diagnosis, WHO grading, molecular information and the final top diagnosis. The term "not otherwise specified" (NOS) entities can be used to describe tumours in which the genetic testing is not performed or molecular results are inconclusive.

The classification of diffusely infiltrating gliomas is substantially changed and based on the presence of mutations in the *IDH1/IDH2* genes and codeletion of 1p/19q. Immunohistochemistry at the protein level for IDH1 R132H expression allows to establish an integrated diagnosis of the majority of diffuse gliomas without performing genetic studies. The mutation of *IDH* is now a decisive marker for classification of diffuse astrocytomas WHO grade II and III, oligodendrogliomas and glioblastomas that arise from lower grade gliomas. Evaluating the morphology there is no basis for distinguishing a fibrillary and protoplasmic subtype of astrocytoma. Only gemistocytic phenotype is considered to be a specific histological variant. Gliomatosis cerebri is an extensively infiltrative growth pattern, not distinct entity. Glioblastomas (GBMs) are divided into 3 groups: glioblastoma IDH-wildtype, which corresponds to clinically-defined primary (de novo) GBM; glioblastoma IDH-mutant, which corresponds to secondary GBM and glioblastomas NOS. A new histological variant - epithelioid glioblastoma was introduced as a rare subtype of GBM with rhabdoid/epithelioid appearance. It occurs most commonly in children and young adults and 50% of cases carry *BRAF V600E* mutation. The term PNET is discarded from the WHO 2016 classification. Diffuse gliomas of the midline with *H3 K27M* mutation has been added as a new entity. Oligodendrogliomas are molecularly defined as diffusely infiltrating gliomas that requires the presence of both *IDH1/IDH2* mutation and 1p/19q codeletion. The designation of oligoastrocytoma is not recommended and remains only as a NOS category. Another subtype of ependymoma *RELA* fusion-positive, typically occurring in

children and young adults, is also incorporated as a distinct variant.

Two new entities have been proposed within the mixed neuronal-glial neoplasms: anaplastic pleomorphic astrocytoma WHO GIII and diffuse leptomeningeal glioneuronal tumour (DLGNT). Anaplastic PXA is characterized by brisk mitotic activity ≥ 5/10 HPF. Over 50% of PXAs carry a *BRAF* point mutation, mostly *V600E*. DLGNT usually reveals oligodendroglial, neuronal and pilocytic features but its clinical course remains unknown. The rosette forming glioneuronal tumour (RGNT) is no longer defined as a fourth ventricle tumour as it may be situated in other brain region and spinal cord. Both these tumours share the same genetic alterations.

Considering meningiomas it is suggested that the brain invasion is a sufficient criterion to recognize an atypical meningioma WHO grade II. Moreover, the new WHO 2016 classification combines the solitary fibrous tumour and hemangiopericytoma into one common entity SFT/HPC. Both these tumours share the same genetic alterations with STAT6 protein accumulation in the nuclei of neoplastic cells.

Diagnostic accuracy of stereotactic needle biopsy without intraoperative neuropathological verification: a 5-year single-center experience

Piotr Murawski[1], Witold Libionka[1,6], Patryk Kurlandt[1], Jakub Wiśniewski[1,7], Stanisław Adamski[1], Ewa Iżycka-Świeszewska[2,3], Blanka Hermann[2,3], Katarzyna Czarnota[2,3], Karolina Gizelbach-Żochowska[2], Ewa Szutowicz[4], Wojciech Kloc[1,5]

[1]Department of Neurosurgery, Copernicus Hospitals, Gdańsk
[2]Department of Pathology and Neuropathology, Medical University of Gdansk, Gdańsk
[3]Department of Pathomorphology, Copernicus Hospitals, Gdańsk
[4]Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdańsk
[5]Department of Neurology and Neurosurgery, University of Varmia & Masuria, Olsztyn
[6]Chair of Rehabilitation and Kinesiology, Gdansk University of Physical Education, Gdańsk
[7]Department of Surgery and Urology for Children and Adolescents, Medical University of Gdansk, Gdańsk

Introduction and aim: With the advance in neuroimaging and introduction of multiple sampling technique in stereotactic biopsy, use of intraoperative histological verification has been questioned. The aim of the study is to assess yield and accuracy of biopsy accommodating this technique, as verified with final histological diagnosis after tumor resection.

Material and methods: Of 141 patients who underwent frame-based stereotactic biopsy between 2013 and 2017, 25, who later underwent open tumor resection, were included in the study. Biopsies were performed under local anesthesia, using Inomed stereotactic system. 4-12 samples were taken from multiple sites within the tumor with side-cutting biopsy cannula. Tissue was inspected macroscopically by the surgeon.

Results: Neoplastic tissue was found in 23 cases (92%). One biopsy revealed necrotic tissue related to the central tumor necrosis on MRI, and another one revealed gliosis. Histological diagnosis showed glioblastoma multiforme (GBM) in 6 cases, grade III glioma in 4, grade II in 12, DNET in 1, necrosis in 1 and gliosis in 1. Final diagnoses in these patients confirmed GBM in all 6 cases, grade III glioma in 3 of 4, grade II in 6 of 12, and DNET in 1 case. GBM was diagnosed in 1 case, previously assessed as grade III, grade III in 3 cases previously diagnosed as grade II and GBM in 3 cases diagnosed as grade II. In 2 patients with necrosis/gliosis, final diagnosis was GBM. No hemorrhagic, infective or neurological complications occurred and all patients were discharged within 24 hours after surgery.

Conclusion: With the proper technique, lack of intraoperative neuropathological examination does not negatively influence diagnostic yield and accuracy of stereotactic biopsy.

Can a low grade tumor catch you by surprise? A case report of an unexpected behavior of a DNT

Dominika Pawełczak[1], Ewelina Sądaj[1], Magdalena Stachura[2], Justyna Rybus[2], Stanisław Kwiatkowski[2], Dariusz Adamek[3]

[1]Jagiellonian University Medical College, Kraków
[2]Department of Pediatric Neurosurgery, University Children's Hospital, Kraków
[3]Department of Pathology, Jagiellonian University Medical College, Kraków

Dysembryoplastic neuroepithelial tumor (DNT) is a WHO grade I glioneuronal brain neoplasm typically occurring in young patients and presenting with intractable epilepsy. Though it has been known to have benign behavior and good outcome following surgical excision, in recent years the matter does not seem as entirely obvious as it used to. Cases of recurrences or histopathological transformations have been reported in literature, questioning the present perception of DNT.

We present a case of a 3 years old girl who presented with a history of drug-resistant focal seizures and left-sided hemiparesis. She underwent a subtotal resection of the lesion located in right frontoparietal area, which revealed typical DNT features on microscopic examination. Nonetheless, 2 years later, the seizures recurred and another surgery was performed with the same histopathological diagnosis. 5 years after the initial surgery the patient started presenting absence seizures and the lesion was reoperated. On following microscopic examination the tumor had different, unclear morphology, corresponding to an "oligodendroglioma-like lesion" or pilocytic astrocytoma [PA]. Eight months later, a new lesion was revealed on MRI, superficial to the site of tumor resection. The lesion had a discoid shape and the histopathological examination lead to diagnosis of a intradural PA "implantation".

This case adds to the growing literature concerning unusual behaviour of DNT, though being an unique example of DNT regrowth with subsequent development of PA. It also indicates that despite typically benign behavior, DNTs may pose a diagnostic and therapeutic challenge that warrants necessity of cautious follow-up.

High grade glioma resection using intraoperative magnetic resonance and 5-ALA imaging

Maciej Racinowski[1], Jakub Wiśniewski[1,2], Patryk Kurlandt[1], Piotr Murawski[1], Witold Libionka[1,7], Stanisław Adamski[1], Ewa Iżycka-Świeszewska[3,4], Blanka Hermann[3,4], Katarzyna Czarnota[3,4], Karolina Gizelbach-Żochowska[3], Ewa Szutowicz[5], Wojciech Kloc[1,6]

[1]Department of Neurosurgery, Copernicus Hospitals, Gdańsk
[2]Department of Surgery and Urology for Children and Adolescents, Medical University of Gdansk, Gdańsk
[3]Department of Pathology and Neuropathology, Medical University of Gdansk, Gdańsk
[4]Department of Pathomorphology, Copernicus Hospitals, Gdańsk
[5]Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdańsk
[6]Department of Neurology and Neurosurgery, University of Warmia and Mazury, Olsztyn, University of Varmia & Masuria University
[7]Chair of Rehabilitation and Kinesiology, Gdansk University of Physical Education, Gdańsk

Introduction and aim: Intraoperative MRI and 5-ALA (5-aminolevulinic acid) induced fluorescence imaging are used to assess completeness of HGG removal. The aim of the study is to assess how intraoperative imaging affects extent of resection and clinical outcome.

Material and methods: Between 2013 and 2017 Medtronic PoleStar N30 iMRI combined with 5-ALA imaging were used in 24 patients (mean age, 55.8 years; range, 21-72) undergoing HGG resection at our institution. 5-ALA (20 mg/kg) was administered 3 hours before surgery. MR image acquisition was performed after positioning and used as reference exam for neuronavigation. Control iMRI was performed after presumed complete tumor resection. If there was remnant tumor mass amenable to surgery, resection was continued until control iMRI confirmed that safety limit had been reached.

Results: In 10 patients tumor involved left, and in 14 patients right hemisphere. In 18 cases first control iMRI confirmed complete (> 95%) tumor resection. In 3 cases tumor remnant was further excised to achieve completeness, and in 3 cases resection of > 85% was considered to reach safety limit. Neuropathologic examination revealed glioblastoma multiforme in 15 patients, anaplastic astrocytoma in 6 and anaplastic oligodendroglioma in 3. Three-month survival was 96%, 6-month 83%, and 12-month 66%. iMRI prolonged operative time (mean 34 minutes). No hemorrhagic, infective or neurological complications occurred.

Conclusions: Combined use of intraoperative magnetic resonance and 5-ALA fluorescence imaging in resection surgery for high grade gliomas provides satisfactory completeness with excellent safety profile.

Brain Tumor Biobanking for the further "omics" analyses. "Brain tumors biobanking as an essential tool for translational medicine development"

Joanna Reszec[1], Anna Michalska-Falkowska[2], Zenon Mariak[3], Sylwia Chludzinska[1], Patrycja Modzelewska[1], Sylwia Chmielewska[1], Jacek Niklinski[2]

[1]Department of Medical Pathomorphology, Medical University of Bialystok
[2]Department of Clinical Molecular Biology, Medical University of Bialystok
[3]Department of Neurosurgery, Medical University of Bialystok

Biobanks collecting high quality human biological material and comprehensive clinical information are becoming crucial organizations in the era of Big Data introduced by medical research. Current standards of novel studies require the highest possible quality of collected biological material to ensure the reliability and reproducibility of analysis. To meet the needs of developing molecu-

lar research, foundation of personalized medicine, unique biobanking system was established at Medical University of Bialystok (MUB), Poland.

Foundation of fully-equipped oncology biobank along with necessary documentation, procedures, and forms was possible on the basis of international collaboration of MUB with Indivumed GmbH and Indivumed Inc., leading biorepository companies in Germany and USA. In order to maintain the highest quality of samples and reproducibility of the research conditions, the Standard Operating Procedures were prepared in accordance with the criteria of Good Laboratory Practice and Good Medical Practice. Each process combined with collection, preparation, and storage of biological material is documented on the forms dedicated to particular operations. Very important type of biospecimens and data collected in MUB's biobank constitutes samples collected from patients with brain tumors. Patient's qualification takes place during consilium of specialists. During conversation with patient, physician introduces the assumptions of MUB's biobanking and patient signs the Patient Informed Consent. Then, study nurse from biobank collects blood and urine from the patient, along with comprehensive interview, e.g. current disease symptoms, comorbidities, medications taken, family history of cancer. Blood and urine are transported to the laboratory within 15 minutes after collection. In laboratory, technician secures the whole blood, serum, plasma, urine supernatant, and urine sediment. In the day of surgery, study nurse is present in the operating room since the beginning of brain tumor resection, which allows to precise record the time of resection start, exact localization of tumor, time of resection end. Just after tumor resection, study nurse is securing the tissue samples, provided by neurosurgeon. Biospecimens collection is documented photographically with the use of millimeter paper and each sample is placed into bar-coded cryotube with anonymized case number and sample number. Then, cryotubes are secured in portable container with liquid nitrogen. Time of cold ischemia between tumor resection and placing the tissue into liquid nitrogen is strictly recorded in the patient form. The biobanks conducts the collection of various type of brain tumors: glioblastomas, meningiomas (grade I, II, and III), as well as orbital tumors. If possible, pathologist or study nurse present in the surgery room, secures samples from the tumor center and tumor margin – this kind of biospecimens provides a special value, because could be used in the studies of tumor heterogeneity.

Brain tumor samples collected under strictly monitored conditions with whole set of clinical data consist the most reliable subject of novel molecular investigations. Studies of cancer genomics, metabolomics, proteomics, microRNA analysis set a new path for biomarker discovery, development of early cancer diagnosis, exploration of drug targets and new molecules for better cancer treatment.

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Subependymomas – our own experience from the last decade

Aleksandra Sejda[1], Blanka Hermann[2,3], Ewa Iżycka-Świeszewska[2,3], Wojciech Wesołowski[4], Wojciech Kloc[5,6], Marek Derenda[7], Waldemar Och[8]

[1]Department of Pathomorphology, Specialistic Hospital, Olsztyn
[2]Department of Pathology and Neuropathology, Medical University of Gdansk, Gdańsk
[3]Department of Pathomorphology, Copernicus Hospitals, Gdańsk
[4]Pathomorphology ELPAT PPL, Elbląg
[5]Department of Neurosurgery, Copernicus Hospitals, Gdańsk
[6]Department of Neurology and Neurosurgery, University of Warmia and Mazury, Olsztyn, University of Varmia & Masuria University
[7]Department of Neurosurgery, Regional Hospital, Elblag
[8]Clinical Department of Neurosurgery, The Voivodal Specialistic Hospital in Olsztyn

Subependymomas are infrequent, slow growing, WHO grade I gliomas that occur predominantly in the proximity of ventricular system. It has been proposed that they derive from subependymal glia, astrocytes of the subependymal plate, ependymal cells or a mixture of astrocytes and ependymocytes. Little is known about their genetic susceptibility, but they are known to be related to trichorhinophalangeal syndrome: an inherited disease caused by mutation in *TRPS1* gene. In recent report *TRSP1* gene alternations were also found in sporadic cases. The treatment of subependymomas is complete surgical resection, which yields a good prognosis.

We present a series of 5 intracranial subependymomas resected in neurosurgery departments in multidisciplinary centers in Elbląg, Gdańsk and Olsztyn. Three patients were females, two males, age range from 32 to 61. One tumor was located in third ventricle, one in fourth, and three in lateral. Clinical symptoms in three patients included: visual disturbances, paraparesis, headache and dizziness. Two tumors were detected incidentally. On MRI scans tumor presented as well-demarcated nodular masses without contrast enhancement. One patient had hydrocephalus. All patients underwent complete tumor resection.

Histologically, all neoplasms were made of clusters of uniform cells with small, round to oval nuclei embedded in a background of fibrillary matrix with common microcystic changes. Nuclear pleomorphism was minimal and mitotic activity was absent. In one case pathologic thick-walled irregular tumor vasculature with hemorrhages and hemosiderin-laden macrophages was noted. All were highly positive for vimentin and GFAP, three were olig2-positive, one case revealed focal EMA-positivity, one case – focal synaptophysin. Neuronal markers and IDH1 were not detected. Proliferation index Ki-67 was below 1% in all cases.

The differential diagnosis of subependymoma includes ependymoma, central neurocytoma, subependymal giant-cell astrocytoma, hemangioblastoma, and glio-neuronal tumors. In our series the histological features and immunophenotype were typical for subependymomas. Diagnostic difficulties created one case with angiomatous component.

Transmissiblity of neurodegenerative diseases – is there a risk of prion-like transmission by neurosurgical procedures?

Beata Sikorska

Department of Molecular Pathology and Neuropathology, Medical University of Lodz

Prion diseases are a group of fatal neurodegenerative disorders, which appear as sporadic, familial and infectious forms. They are caused by an infectious agent known as a "prion" which is widely regarded to be an aggregate of an abnormal isoform (PrP^{Sc}) of a normal cellular glycoprotein (PrP^{c}). There are several protein misfolding disorders – the most widely known include Alzheiemer disease, Parkinson disease and other α-synucleinopathies, ALS, frontotemporal dementias, polyglutamine expansion diseases such as Huntington disease and certain spinocerebellar ataxias. The proteins involved in any of those are different (amyloid-beta; alpha-synuclein; MAPTtau, and huntingtin) but the molecular mechanism is almost exactly the same, a seeding-nucleation mechanism. There is an increasing body of evidence to indicate that the abnormal protein aggregates in these diseases exhibit prion-like properties and can spread through the CNS. Recent reports of Aβ accumulation in the CNS in patients with iatrogenic Creutzfeldt-Jakob disease caused by human pituitary-derived growth hormone or dura graft have suggested that Aβ may also have been transmitted iatrogenically in these patients. These findings raise the question about safety of neurosurgical procedures including potential exposure to Aβ, in the reuse of Aβ-contaminated neurosurgical instruments, or via blood transfusions from elderly donors.

Pediatric brain tumors: the molecular profile and new insight in clinical approach

Joanna Trubicka

Department of Pathology, The Children's Memorial Health Institute, Warsaw

Brain tumours belong to the most common solid childhood tumours and are the main cause of cancer-related death in children. In the past decade we observed remarkable progress in understanding the molecular background of common childhood cancers such as medulloblastoma and glioma. Advances in genomics and epigenomics have provided insight into the molecular heterogeneity of these diseases and revealed diagnostic markers which increased ability to predict patient outcomes, for example, identifying favorable prognosis associated with WNT-MB group in medulloblastoma and the poor outcomes associated with mutation in *H3F3A* (p.K27M) in glioblastoma patients, G3-MB and SHH-MB with *TP53* mutation in medulloblastoma, and PF-EPN-A in ependymoma. Genomic studies have revealed also mutations in key oncogenic drivers regulating various signaling pathways, which may present new opportunities for targeted therapeutic intervention. We demonstrated a review of the most important molecular markers for pediatric brain tumours and their implications for patients stratifications and improvement of therapy. We presented also recently published data indicating that germline mutation in DNA-repair genes are associated with occurrence of rare severe adverse effects during chemotherapy in children.

Contemporary management of pituitary tumors

Grzegorz Zieliński[1], Maria Maksymowicz[2]

[1]Department of Neurosurgery, Military Institute of Medicine, Warsaw
[2]Department of Pathology and Laboratory Diagnostics, M. Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw

Pituitary adenomas (PAs) are benign, slow growing neoplasms arising from adenohypophysial cells. They account for nearly 20% of all intracranial tumors. PAs

may extend beyond the sella and invade cavernous sinus and suprasellar cisterns. They may produce mass effects on surrounding structures, especially on optic chiasm. PAs are classified as functioning and non-functioning on whether excess hormone secretion can be clinically identified. Functioning PAs produce typical clinical syndromes, e.g. acromegaly, Cushing's disease etc. MRI is the method of choice in the imaging of pituitary tumors. Pituitary surgery is the first line treatment in most of pituitary tumors except PRL-secreting adenomas which should be treated pharmacologically. Five-tier classification of PAs is preferred by pathologist for tumors categorization. This method takes into consideration the clinical and laboratory findings, imaging results, histologic, immunocytochemical and ultrastructural features of tumor cells. Currently, there is no possibility to predict the likelihood of adenoma recurrence. Therefore, the 2017 WHO classification of tumors of the pituitary gland: (1) introduces a novel approach to classifying pituitary tumors according cell lineages, (2) changes the histological grading, (3) proposes a new group of the tumors with clinical aggressive behavior – "high-risk pituitary adenomas" and (4) defines a group of the tumors with thyroid transcription factor-1 expression. It is hoped that new classification allows to better diagnose pituitary tumors and to understand their biological and clinical behavior.