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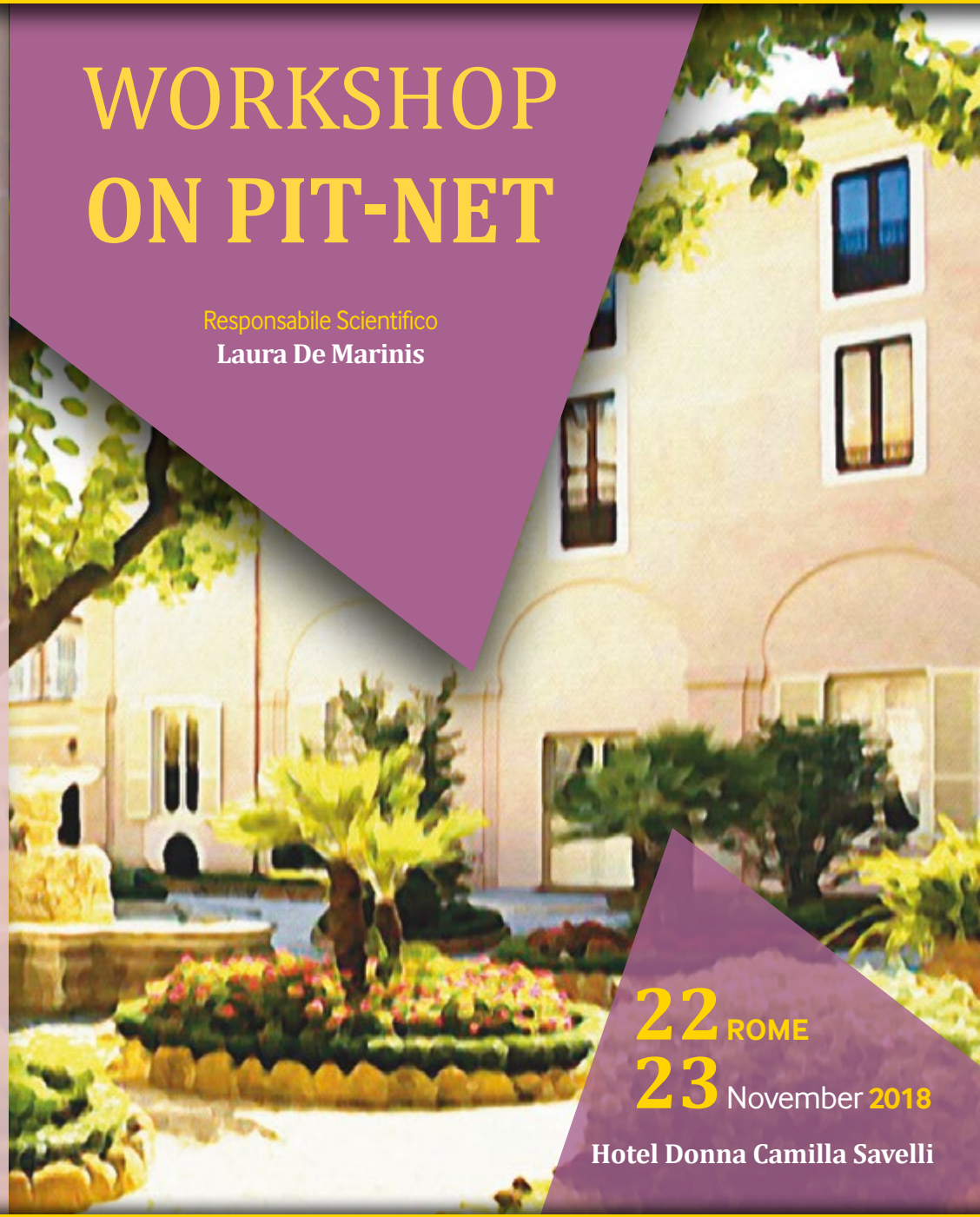
WORKSHOP ON PIT-NET

Responsabile Scientifico
Laura De Marinis



22 ROME
23 November 2018

Hotel Donna Camilla Savelli

1st DAY | *Thursday, 22nd* November 2018

PRESIDENTIAL LECTURE

Chairmen: **A. Lenzi, A. Pontecorvi**

Andrea Giustina

Professor of Endocrinology and Metabolism, Università Vita e Salute San Raffaele - Milan, Italy

"New Acromegaly guidelines"

The 11th Acromegaly Consensus Conference was held in April 2017with the goal of optimizing clinical practice in the management of acromegaly and updated recommendations on therapeutic outcomes for patients with acromegaly which have recently been published in Nature Reviews Endocrinology. The previous Consensus guidelines on the medical management of acromegaly were published in 2014; since then, new pharmacological agents have been developed (Pasireotide) and new approaches to treatment sequencing and combination with somatostatin analogs and pegvisomant) have been considered. More than 30 experts in the management of acromegaly reviewed the current literature and assessed results and side effects of available pharmacologic treatments. Among the treatment outcome goals were considered biochemical, clinical, tumour mass and surgical outcomes. The participants discussed first, second and third line pharmacological choices and their determinants. As a result of this discussion, through a grading of available evidences, for each agent a specific place in the new guidelines has been proposed.

I SESSION

Chairmen: **A. M. Colao, S. Nanni, G. Rindi**

Jacqueline Trouillas

Professeur Emérite, Faculty of Medicine Lyon-Est, University of Lyon1 - Lyon, France

"Classification of PIT-NET"

Pituitary adenomas, recently renamed Pituitary NeuroEndocrine Tumors (PitNET)s, and integrated in the NeuroEndocrine Tumors (NET)s, are common intracranial tumors, originated from the adenohypophysis.
Historically, they have been considered to be benign and treated as an endocrinological disease. However, many are invasive and some of them exhibit aggressive behavior and, exceptionally, metastasis (carcinoma). Recently, it has been suggested that aggressive

tumors and carcinoma are two sides of the same coin.
In this talk, I will present a critical review of the PitNET classifications, focusing on a prognostic five-tiered clinicopathological classification, which integrates invasion assessment by imaging, the immunohistological subtype (somatotroph, lactotroph, thyrotroph, corticotroph, gonadotroph), and the proliferation status (mitotic count, Ki-67 and p53 indexes). Some molecular and genetic markers that have been related to tumor behavior, and theranostic factors (such as expression of the somatostatin and estrogen receptors) related to the response to medical treatment, will be also presented.
Nowadays, a multimodal approach taking into account histopathological, radiological and molecular markers may identify "tumors with malignant potential", requiring careful follow-up. The management of patients with PitNETs must be multidisciplinary, including clinicians (endocrinologist and neurosurgeon), radiologist, and pathologist.

Federico Roncaroli
Faculty of Biology, Medicine and Health
University of Manchester – Manchester, United Kingdom

"How and when a pituitary NET should to be considered aggressive?"

Division of Neuroscience and Experimental Psychology, Faculty of Biology, Medicine and Health, University of Manchester – United Kingdom
The identification of pituitary adenomas or PiNET that are likely to recur and metastasise is one of the most challenging problems in pituitary pathology1. Clinical and neuroimaging criteria including extension to cavernous sinuses and bone invasion are currently regarded as more reliable prognostic biomarkers than pathological features2 reflecting on treatment strategies3.
The 2017 WHO classification of Pituitary Tumours has removed the definition of "atypical adenoma" leaving a void in the diagnosis of those PitNets that may have aggressive potential and suggested that outcome is predicted more accurately by the histotype1. This position remains controversial. The definition of carcinoma remained unchanged, still requiring the presence of metastases. It must be remembered that "atypical adenoma" is the contraction of the descriptive definition of "adenoma with uncertain malignant potential" originally introduced by Pernicone et al in 19974. This definition was not meant to establish an entity but was intended to warn clinician of the possibility of a more aggressive behaviour.
A myriad of biomarkers have been proposed over the last 20 years, but only mitotic count and proliferation index measured with MIB-1 seem to offer to good reproducibility and good prognostic power. Although it requires further validation, the most reasonable attempt so far to provide clinicians with a prognostic indicator has been proposed by Trouillas and colleagues in 20135. This 5-tier approach combines pathological features including mitotic count, MIB-1 labelling index and p53 status with the extension of the tumour.

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Marco Losa
Dept. of Neurosurgery, Istituto Scientifico San Raffaele, University Vita-Salute - Milan, Italy

"Italian Experience"

Pituitary carcinomas and aggressive pituitary adenomas not responding to standard surgical, medical, and radiation treatments may respond to chemotherapy with temozolomide. The drug is an oral second-generation alkylating agent that depletes the DNA repair enzyme O6-methylguanine-DNA methyltransferase (MGMT) in various cell types. The drug penetrates the blood-brain barrier and has antineoplastic activity against high-grade gliomas. Following preliminary reports that demonstrated a good response to temozolomide treatment in patients with either pituitary carcinoma or aggressive pituitary adenomas, larger series on this topic have appeared in the literature.
In a multicenter study performed among Italian endocrinologists, we collected the clinical data on 31 patients who had been treated with temozolomide. Among the various subtypes of pituitary adenomas treated with temozolomide, there seems to be a relative paucity of patients with acromegaly. The majority of patients had a response to temozolomide that consisted in a significant reduction of tumor size or stabilization of tumor growth, while about 30% of patients experienced progression of disease. Temozolomide was generally well tolerated and no serious side effects were reported.
Temozolomide has demonstrated value in the treatment of pituitary carcinomas and aggressive adenomas resistant to standard therapies.

II SESSION

Chairmen: **A. Farsetti, A. M. Isidori, V. Toscano**

Ettore Domenico Capoluongo

Professor and Head of Laboratory, Head of Laboratory of Clinical Molecular and Personalized Diagnostics, A. Gemelli Foundation – Rome, Italy

"PIT-NET from genetic to clinical"

Pituitary adenomas (PA) are relatively common condition, estimated to be present overall in 17% of the general population. Clinically relevant pituitary adenomas are present in 0.1% of the general population, and they represent the third most-frequent intracranial tumor type after meningiomas and gliomas.
PA are monoclonal neoplasms in origin, where a number of different molecular mechanisms leading to this condition have been described, although in the majority of the sporadic cases, the exact molecular pathogenesis still remains unknown.
Factors hypothesized to contribute to pituitary neoplasia initiation and proliferation include:

- altered growth factors and cell-cycle regulators that are the result of epigenetic changes
- abnormal hormonal milieu
- abnormal intrapituitary microenvironment
- Inherited or somatic mutations

The present talk will focus on th following topics:

a. Heterogeneity of Pituitary Adenomas (PA)
b. Molecular aspects of PA
c. DIfferent diagnostic approaches
d. MEN-1 syndromes
e. Data on MEN-1 provided by our group.

A detailed description of molecular alterations surroungind the Isolated familial pituitary adenomas (FIPA) will be provided. FIPA corresponds to the presence of PA in two or more family members with no other syndromic features present. FIPA is a heterogeneous condition, including patients with mutations in the:

- aryl hydrocarbon receptor– interacting protein (AIP) gene
- pts with X-linked acrogigantism (XLAG) due to duplication of GPR101
- pts with a family history of pituitary adenomas with no known genetic cause Furthermore, Syndromic pituitary adenomas in the context of MEN1 syndrome represents an important pattern needing molecular diagnostic support. MEN1 is characterized by the presence of the classical triad of:

a. hyperparathyroidism (in almost all patients by the age of 50 yrs
b. Pituitary adenomas (in about 30%–40% of cases)
c. Neuroendocrine tumors (in about 60% of cases)

MENIN plays an important role in:

- G1–S checkpoint regulation
- response to DNA damage and apoptosis
- regulation of histone deacetylation and methyl transferase complexes
- interaction with transcription factors and nuclear receptors (as well as transport of b-catenin)

Finally, an updated description of germline and somatic genetic pattern will be reported for MEN4 and Carney complex, also highlighting the importance of molecular testing as a tool of differential diagnosis.
The setting will be both translational and clinically diagnostic oriented in order to guide the audience to understand what are the main evidence useful in clinical setting.

Francesco Ferraù

PhD in Endocrinological and Experimental Metabolic Sciences, Department of Human Pathology of Adult and Evolutive Age "G. Barresi", University of Messina – Messina, Italy

"The aryl-hydrocarbon receptor role in pituitary physiology and pituitary-NET"

The aryl hydrocarbon receptor (AHR) is a ligand activated transcription factor best known to be involved in cellular detoxification mechanisms. Several studies have shown that AHR plays an important role in cell physiology, independently of its activity as a xenobiotic receptor, being involved also in inflammation, immunity and tumorigenesis. Within the pituitary, AHR activation by environmental toxins has been mainly implicated in disruption of the hypothalamic-pituitary-gonadal axis and fertility, but AHR is also known to have a more complex impact on pituitary hormones synthesis and secretion. Moreover, AHR could also play a role in pituitary cell proliferation and tumour formation, directly or indirectly via the interaction with other cellular signalling pathways. Overall, within the pituitary, evidences suggest that AHR contributes to regulate endocrine signalling, cell proliferation and to mediate the disruptive effect of environmental toxins, potentially impacting on pituitary tumours' pathophysiology and clinical expression.

2nd DAY | *Friday, 23rd* November 2018

III SESSION

Chairmen: **G. Mantovani, P. Zuppi**

Antonio Bianchi

Pituitary Unit, Department of Endocrinology,
Catholic University of the Sacred Heart – Rome, Italy

"PIT-NET from histological feature to clinical"

The 2004 WHO classification of neoplasms of adenohypophysial cells was misleading for different reasons: the simplistic distinction between adenoma and carcinoma, based solely on metastatic spread; the poor reproducibility and predictive value of the definition of atypical adenomas based on the detection of mitoses or expression of Ki-67 or p53; the difficulty to accurately reflect the clinical spectrum of behavior of these lesion.
In real life, pituitary adenomas are associated with a spectrum of variable clinical, biochemical and radiologic features and differing therapeutic outcomes. Invasion and regrowth of proliferative lesions and persistence of hormone hypersecretion cause significant morbidity and mortality.
The new WHO 2017 clinicopathological classification of pituitary endocrine tumours included the following main changes: a novel approach for classifying pituitary neuroendocrine tumors according to pituitary adenohypophyseal cell lineages; changes to the histological grading of pituitary neuroendocrine tumors with the elimination of the term "atypical adenoma.
However, one of the misleading in this current classification is a simplistic distinction between adenoma and carcinoma. In 2017, the International Pituitary Pathology Club proposed a new terminology, pituitary neuroendocrine tumor (PitNET), which is consistent with that used for other neuroendocrine neoplasms and which recognizes the highly variable impact of these tumors on patients. Our experience and our preliminary data (here exposed) confirm that pituitary neuroendocrine tumors are not simply endocrine diseases, but should be considered as tumors with endocrine manifestations within the context of oncology.

Antonella Giampietro

MD, Simple Operative Unit of Hypothalamus-Pituitary Pathology
Catholic University of the Sacred Heart, A. Gemelli Foundation – Rome, Italy

"Hypopituitarism in PIT-NET"

Hypopituitarism is a potentially severe medical condition characterized by defective secretion of some or all (panhypopituitarism) of the pituitary hormones. The resulting pituitary hormone deficiencies may lead to severe clinical consequences with significant morbidity and often increased mortality despite recent therapeutic improvements. A major issue in the diagnostic workup of anterior pituitary hormone deficiency is the identification of the cause of hormone dysfunction that may be related to several different mechanism. Anterior pituitary hormone deficiencies may be secondary to any lesion in the sellar or suprasellar region, most commonly benign tumors such as pituitary adenomas or craniopharyngiomas. Surgical or radiation-based treatment of these tumors are also a common cause of hypopituitarism. Less frequently, cranial traumas, inflammatory or autoimmune process such as lymphocitic hypophysitis or genetic defects may lead to pituitary deficits. Hypopituitarism, however, remains predominantly a consequence of benign pituitary tumors and of their treatments. These disorders represent a heterogenous group of rare diseases leading to defective function of specific pituitary cell types. Syntoms related to tumor mass such as headaches and visual defects may represent the initial presenting syntoms, given that syntoms of hypopituitarism are frequent overlooked due to their gradual onset and unspecific nature (asthenia, dry skin, loss of libido). The gonadal axis is the most commonly affected (77%), followed by the adrenal (28%) and thyroid (22%) axes. In most series, GH secretion has not been formally evaluated, but a recent study reported a 77% rate of GH deficiency. If normal pituitary tissue remains viable, surgical decompression may lead to reversal of hypopituitarism. The likelihood of recovery of pituitary function is less common in NFPAs compared with functioning adenomas and depends on accessibility, aggressiveness, size of the tumor, skill of the surgical team and the chosen operative pathway. Craniopharyngiomas that grow aggressively and are difficult to access, lead to worse results. Proper recognition of pituitary hormone deficits is of critical importance in the workup of any patient with hypopituitary lesions because overlooked hormone deficiencies may lead to severe clinical consequences, including a risk of fatal outcome especially in case of unrecognized corticotroph deficency. Diagnosis and treatment of patient with hypopituitarism needs careful clinical evaluation and individual optimization, taking into account that this goal is hardly obtained by currently available treatments.

LECTURE

Chairmen: **C. Scaroni, M.C. Zatelli**

Marta Korbonits

Barts and the London School of Medicine, QMUL - London, United Kingdom

"Genetics entering the pituitary clinics - New era, new problems"

Genetic testing is becoming more and more integral part of the endocrine and especially the pituitary clinic with the myriad causes of congenital hypopituitarism and the increasing number of diseases predisposing for pituitary tumours. Prevention of disease or severe complications is the key goal of modern medicine. The practicing endocrinologist needs to get grips with the potential power and information of genetics and

needs to understand the information coming back from the genetic lab.
Genetic testing should only be recommended if there is either evidence or logical support that it will reduce morbidity or mortality for the patient or other family members. Often the benefit of testing will be rather in cascade family screening of (to date) unaffected individuals than in the patient itself. In other cases, there are treatment decisions that are influenced by genetic testing.
Understanding the various genetic terms are crucial for the interpretation of the test result and the correct advice for the patient. For example, was there sequencing of the whole gene done or just the exons and exon-intron boundaries? Was there a test performed for copy number variation? Were other genes causing similar disease also tested (panel testing)? Are the patterns in the disease inheritance compatible with imprinting or mitochondrial DNA inheritance? The power of newer types of genetic testing also brings the problem of interpretation of rare variants into the clinical setting. Characteristic genetic issues will be illustrated with examples from characteristic endocrine genetic diseases.

IV SESSION: DIAGNOSIS

Chairmen: **M. G. Brizi, C. Colosimo, A. Lania**

Tommaso Tartaglione
Director of the Complex Operating Unit of Radiology and Diagnostic Imaging, "I.D.I."- Rome, Italy

"Neuroradiology in PIT-NET"

Magnetic Resonance Imaging (MRI) represent the gold-standard technique for studying hypothalamus-pituitary region and should always conducted in cases of pituitary pathologies, less than major contraindication to MRI.
The neuroradiologist plays a crucial role in the multidisciplinary management of these patients, thought the morphological diagnosis of the pituitary adenoma, the definition of aggressiveness according to the evaluation of pituitary adenoma's dimension, extension, local invasiveness and, in rare cases, of systemic metastasis, prevalently located at the bone marrow.
With regard to morphological diagnosis, pituitary adenomas are at the neuroimaging study classified as small pituitary adenoma (in cases of lesion < 10 mm), large pituitary adenoma (in cases of lesion > 10 mm). Some authors suggest the term "giant pituitary adenoma" when the lesion maximum diameter is > 40 mm. Small pituitary adenomas are typically located within the sell as intrasellar mass, appear as circumscribed, well –demarcated mass surrounded by crescentic rim of compressed anterior pituitary, typically slightly hypointense to pituitary gland in T1weighed imaging, isointense in T2-weighed. In contrasted T1 weighted imaging, small pituitary adenomas appear in around 70-90% of cases as hypointense, compared to the intense enhancement of the pituitary gland and of the cavernous sinus and generally enhance more slowly than adjacent normal pituitary. Dynamic contrasted-enhanced thin-section T1-weighted images may be of great usefulness in cases of small lesion. This method represents the best way for detecting small pituitary lesions, that in around 10-30% of cases can be identified only with this procedure. Large and giant pituitary adenomas show in most cases a supra-sellar or para-sellar extension and appear usually isointense with gray matter in T1 and T2-weighed images. Although cavernous sinus invasion is sometimes difficult to define, the presence of tumoral tissue between the cavernous carotid artery and the lateral dura is considered a sign of cavernous sinus invasion and quantization attempts has been proven, particularly to Knosp classification. At least, giant pituitary adenomas may invade skull base, extending into anterior, middle and posterior fossa, clivus, 3rd ventricle or infundibulum and sphenoid sinus .
Moreover, neuroradiologist can identify prognostic marker of response to the treatment as well as he can define the treatment outcome, after neurosurgery, drugs or radiotherapy, also according to hormonal features.
Particularly, seriate MR examinations can easily evaluate treatment response in Patients with PRL-adenoma treated with medical therapy. Similarly, hyperintense T2-weighed in GH secreting pituitary adenomas and larger pituitary GH adenoma's dimensions are associated to a worse outcome of treatment with somatostatin analogues, also as post-surgery treatment. Larger pituitary adenoma's residual after pituitary neurosurgery is associated to a poor response also to treatment with Pegvisomant, a growth hormone receptor antagonist.
In conclusion, neuro-radiological features have to be considered and integrated to genetic, molecular and clinical characters of each patient for a multidisciplinary patient management and for a personalized therapy.

Vittoria Rufini
Nuclear Medicine Unit, Catholic University of the Sacred Heart, A. Gemelli Foundation – Rome, Italy

S. Taralli, M. Lorusso
Nuclear Medicine Unit, A. Gemelli Foundation - Rome, Italy

"How the nuclear medicine can improve the diagnosis and management of PIT-NET?"

The role of nuclear medicine in the diagnostic management of pituitary endocrine tumors is still not well established. Many tracers are available, which are characterized by different uptake mechanisms reflecting different biologic properties of endocrine cells, potentially playing a role in different clinical scenarios. Among conventional nuclear medicine tracers, 111In-DTPA-octreotide, a marker of somatostatin receptors, is used for single photon emission tomography (SPET) imaging. For positron emission tomography (PET) imaging, the most used tracers for functional evaluation of pituitary endocrine tumors are: 18F-fluorodeoxyglucose (18F-FDG), whose uptake mechanisms

reflect glucose metabolism; 11C-mehionine, reflecting protein synthesis; and 68Ga-somatostatin analogs, reflecting somatostatin receptor expression.
Potential areas of application of functional imaging techniques are: 1) detection of pituitary endocrine tumors prior to surgery, when magnetic resonance imaging (MRI) is equivocal (see microadenomas); 2) detection of residual tumor and tumor recurrence; 3) prediction of malignant potential; 4) eligibility for treatment with somatostatin analogs; 5) response to therapy.
In the future, the wider spread of PET-MRI technology will allow to simultaneously benefit from the high sensitivity and specificity of PET tracers and the high detail for soft-tissues of MRI, thus improving the diagnostic approach of pituitary endocrine tumors.

Alessandro Pedicelli

Director of the Simple Operative Unit of Interventional Neuroradiology Catholic University of the Sacred Heart, A. Gemelli Foundation – Rome, Italy

"How the interventional radiology can improve the diagnosis of Cushing?"

Talking about bilateral inferior petrosal sinus sampling (BIPSS).
Angiographic technique used when non invasive examinations and tests are not diagnostic. It permits direct measure of hormonal pituitary output for diagnosis of ectopic ACTH syndrome with high sensitivity and specificity in determining presence and lateralization of the tumor. Limits: risks related to the invasive procedure, but with low rate of adverse events; possible anatomical difficulties to navigate angiographic catheters and anatomical variants of petrosal sinuses drainage.

V SESSION: MEDICAL TREATMENT

Chairmen: **G. Ferone, P. Gargiulo, S. Grottoli**

Gherardo Mazziotti

Endocrine Unit, A.S.S.T. Carlo Poma of Mantua - Mantua, Italy

"Acromegaly: SSA"

Somatostatin receptor ligands (SRLs) play a major role in medical treatment of acromegaly, the strong rationale being based on their ability to interact with specific receptors on pituitary tumor by which both hormone hypersecretion and tumor growth are controlled. First generation SRLs, octreotide long-acting repeatable (OCT-LAR) and lanreotide autogel (LAN-ATG), are usually used as first-line medical therapy in patients with persistently active acromegaly after unsuccessfully neurosurgical intervention (1). However, over the last two decades, OCT-LAR and LAN-ATG have been also used as first-line therapy in naïve patients with low chances to be cured by neurosurgery (2), based this approach on the rapid effects of these drugs in controlling hormonal hypersecretion and tumor growth (3,4). Another emerging aspect concerns the use of OCT-LAR and LAN-ATG either at doses higher than the conventional regimens (5,6) or in combination with pegvisomant (7,8) to improve control of acromegaly in patients with no fully response to SRLs. Indeed, the current guidelines suggest increasing the dose of the SRLs and/or increasing the dose frequency of LAN-ATG should be attempted when the biochemical control of acromegaly is partial (1). Moreover, in patients with discordant response to SRLs (i.e., tumor shrinkage without biochemical control of acromegaly) and clinically relevant residual tumor, combination treatment with SRLs plus pegvisomant might be proposed (9). The final emerging aspect concerns the use in clinical practice of the new generation SRL, pasireotide LAR, which has been found to be more effective than OCT-LAR and LAN-ATG (10,11). A peculiarity of pasireotide is related to its ability to specifically interact with four out five subtypes of somatostatin receptors (in particular with subtype 5) allowing this drug to be effective to control acromegaly even in patients resistant to first generation SRLs. However, the peculiar affinity receptor profile makes pasireotide prone to negatively influence glucose metabolism. As a matter of fact, an impairment of glucose homeostasis has been consistently reported in acromegaly patients treated with pasireotide LAR (10-12). According to the current guidelines (1), the use of pasireotide LAR in clinical practice should individualized on the basis of the presence or absence of clinically relevant residual tumor and impaired glucose tolerance. In conclusion, after three decades from their appearance in the pharmacotherapy scenario, SRLs are still the mainstay for treatment of acromegaly and new emerging therapeutic approaches have been developed and proposed to improve their effectiveness in real-life clinical practice.

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Pietro Maffei
MD, 3rd Medical Clinic, DIMED, Padua Hospital – Padua, Italy

"Acromegaly: Peg-V"

Pegvisomant (PEGV), a growth hormone receptor antagonist, is one of the most widely used therapy for acromegaly. PEGV is indicated for treatment of patients with resistant acromegaly and to date it is the most effective medical treatment although its costs remain high.
PEGV monotherapy administered as second line therapy achieved a biochemical control rate of 90% or more in clinical trials. However, the real-world data showed that the effectiveness of PEGV is not as high as reported in interventional studies. PEGV effectiveness improves when up titration is appropriate. Higher PEGV doses at start and a more rapid up-titration are necessary in patients with obesity and/or IGF-1 > 2.7 × ULN. The d3-GHR polymorphism it is not of added value for either the prediction of PEGV responsiveness or the determination of the required PEGV dose. Recently, it has been observed that the centers in which more patients are treated with PEGV, less adverse events are reported, but the long-term effectiveness is lower than in centers with less cases, perhaps because of an inadequate patient's selection.
According to the last Consensus Statement (2018), in second-line medical therapy if there is pre- existing clinically relevant impaired glucose metabolism, patients should be switched from first generation somatostatin to PEGV. Furthermore, in the case of clinically relevant residual tumour and pre-existing impaired glucose metabolism, maintaining first-generation somatostatin and adding PEGV is recommended.

AIP mutations are found in 20-25% cases and cause aggressive somatotropinomas, often resistant to somatostatin analogues. AIP-associated tumours can be resistant to management with somatostatin analogues. PEGVS can safely be used, to normalize IGF-1 levels and help control disease also in resistant paediatric somatotropinomas.
ACROSTUDY was initiated in 2004 to serve as an international, post-authorization, safety surveillance study and was open to all patients with acromegaly treated with PEGV. At the second interim analysis of 2090 patients (May 2016) the percentage of patients with normal IGFI levels increased to 73% at year 10, and the average daily dose of PEGV increased from 12.8 mg (year 1) to 18.9 mg (year 10). Locally reported MRIs showed most patients (72.2%) had no change in tumor size; 16.8% had a decrease, 6.8% an increase, and 4.3% both. PEGV inhibits the secretion of GH and PRL in primary cultures of human GH(/PRL)-secreting pituitary adenomas without effect on cell viability or cell proliferation. Treatment patterns changed over the 10-year period, with recent patients more likely to receive any combination therapy (20% in 2003 vs 54% in 2012). In addition, combo somatostatin and PEGV use varied widely among countries from 22% to 78%. The combination treatment with somatostatin and PEGV appears to reduce the required dose of PEGV. At the second interim analysis of 2016, adverse events or serious adverse events treatment related, were reported in 16.1% and 2.3% of patients respectively. Patients who need more PEGV to normalize IGF-I are usually younger, have higher baseline IGF-I levels, more hypertension, more sleep apnea and diabetes and are more overweight.

Sabrina Chiloiro
Simple Operative Unit of Hypothalamus-Pituitary Pathology,
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"Prolactinoma"

Prolactinomas represent the most common hormone-secreting pituitary tumors (up to 40% of all pituitary tumors), with the incidence being 6-10 cases per million people per year and an estimated prevalence of 100 per million people in adults. In women, microadenomas are more frequent than macroadenomas, whereas in men macroadenomas are prevalent. In the pediatric and adolescent age, prolactinomas are rare, but represent about half of all pituitary adenomas, which overall account for less than 2% of intracranial tumors. Clinical manifestations of prolactinoma are related to the serum prolactin elevation and to the tumor mass effect. Consequently, the aim of the prolactinoma treatment is to restore from the effects of both hyperprolactinemia and tumor mass. Nowadays, medical treatment of prolactinomas is basically performed using dopamine agonists (Das), mainly cabergoline (CAB). Responsiveness to CAB is higher than that to other DA both in macroprolactinomas and in micro-prolactinomas, as well as in non-tumoural hyperprolactinemia. CAB in fact can induce a PRL level normalization in around 80-90% of cases and a reduction greater than 20% of baseline tumor size has been reported in more than 80% of cases. However, long term follow-up

data are crucial for investigate the patient's outcome after the withdrawal of CAB. In fact, persistence of normal value of PRL range between 36 to 67% in cases of micro-adenomas and between 8 to 57% in cases of macro-adenoma. Recurrence rate seem to be influenced by duration of CAB treatment, prolactin value obtained though the lowest dose of DA (is 0.25 mg/week of cabergoline) and percentage of tumor volume shrinkage. Interestingly, among patients affected by micro-prolactinoma, also the patient's age at disease diagnosis, both the baseline PRL value and maximal tumor diameter are able to predict the prolactinoma recurrence risk, after the withdrawal of DA. CAB is considered a safe and well tolerated treatment. Although rarely detected, the main safety issue is related to the potential risk of developing clinically relevant valvulopathy following treatment with CAB. Adverse events more common are nausea, headache, dizziness, nasal congestion and constipation. Moreover, although rare, resistance to DA can occurred in around 11% of cases. Resistance to DA is defined by the failure to achieve normal PRL or to reduce its levels by 50%, by the failure to induce ovulation in women or to reduce symptoms despite CAB dose higher than 2 mg/weekly. These patients are considered candidate to neurosurgical removal of the pituitary adenoma. According to the different series, remission of the disease can be reached in around 80% of micro-prolactinoma and 40% of macro-prolactinoma. Moreover, other conditions can suggest surgery as good therapeutic option, such as the increase of tumor size or persistence of optical chiasma compression, despite optimal medical therapy, the cystic nature of the lesion, the risk of cerebrospinal fluid leak, the occurrence of adenoma apoplexy, the intolerance to DAs. According to the tumor characteristics, surgical resection rather than medical management of the prolactinoma should be discussed with the patient by an endocrinologist and neurosurgery large experienced and multidisciplinary team, evaluating both the risks, the benefits and the alternatives. Patients carried aggressive PRL-secreting pituitary tumors or carcinomas required second line treatments, such us somatostatin analogues or temozolomide, in more limited cases. Recent evidence suggest also a potential use of pasireotide in the treatment of aggressive types of prolactinoma.

Rosario Pivonello

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"Cushing"

A prompt treatment should be performed in Cushing's disease (CD) in order to reduce mortality. CD first-line treatment is represented by pituitary neurosurgery, whereas second-line treatment includes repeated pituitary neurosurgery, radiotherapy, bilateral adrenalectomy and medical therapy. In recent years, the role of medical therapy has been considerably increased, due to the development of novel drugs able to control cortisol excess. Three different categories of drugs may be used in the treatment of CD, including adrenal-directed drugs, pituitary-directed drugs, and glucocorticoid receptor-directed drugs. Among the adrenal-directed drug, the classical ketoconazole and metyrapone induce cortisol normalization in 60-70% of CD patients, although associated to adverse events like liver enzymes elevation and male hypogonadism for ketoconazole, and hirsutism, hypertension and hypokalemia for metyrapone. Mifepristone, the most common glucocorticoid receptor-directed agent, improved the clinical status in 85-90% of patients, but monitoring its efficacy might be difficult for the lack of a biochemical markers, and adverse events include vaginal bleeding, hypokalemia and hypertension. Among pituitary-directed drugs, cabergoline, a potent dopamine agonist, has been shown to be effective in 75% of patients in short-term treatment, and 40-50% in long-term treatment, with around 25% of treatment escape but good tolerance profile. The most recent pituitary-directed drug, pasireotide was demonstrated in phase III clinical trial on 162 patients with CD to induce cortisol normalization in 14.6% of patients (600 µg bid) and 26.3% (900 µg bid) after 6 months and in 13.4% (600 µg bid) and 25% of patients (900 µg bid) after 12 months. The safety profile of pasireotide was similar to that of the first-generation SSAs, except for the increased frequency and degree of hyperglycemia. Many advances have been performed in the field of medical therapies and new compounds have been investigated. Osilodrostat is a new adrenal directed drug, which exerts a blocking action of 11β-hydroxilase enzyme, by consequently reducing cortisol synthesis, representing a novel and potential new treatment for CD, orally administered at 2-50 mg twice daily. Data from phase II studies have shown that osilodrostat induced remission rates, in terms of cortisol excess control, ranging from 78.9% to 91.7%. Most common adverse events are hypertension and hyperandrogenism. Pasireotide long acting release (LAR), a new formulation with monthly administration at a dosage of 10-30 mg have recently shown in a phase III clinical trial to induce cortisol normalization in 35% of patients (10 mg) and 25% of patients (30 mg) after 12 months, with similar safety profile of daily pasireotide. New compounds, including levoketoconazole, which is more potent isomer of ketoconazole, and relacorilant, a selective cortisol modulator, are presently under investigation.

VI SESSION: SURGERY AND RADIOTHERAPY

Chairmen: **C. Anile, R. Baldelli, M. Losa**

Francesco Doglietto

MD, PhD Neurosurgery, Department of Medical and Surgical Specialties Radiological Sciences and Public Health, University of Brescia – Brescia, Italy

"The neurosurgeon treatment of PIT-NET"

The recent new classification of "pituitary adenomas" underscores the difficulty of classifying pituitary tumors from a pure anatomo-pathological point of view.
Neurosurgery has evolved significantly in the past two decades with the advent of endoscopy, which allows better visualization of the sellar and parasellar area during surgery. This evolution has led to improved surgical results but also to potential new data that will possibly lead to an increased understanding of pituitary tumors in a multidisciplinary and possibly multicenter approach to this challenging pathology.

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"The radio-therapeutic treatment of PIT-NET"

Radiotherapy is generally used in patients with resistant GH-secreting with the aim of controlling tumor growth and normalizing elevated hormone levels. While conventional radiotherapy (CRT) has been largely employed in such tumors, stereotactic techniques of irradiation have been recently employed with the hope of minimizing the long term toxicity and effectiveness of treatment. Stereotactic irradiation can be given as single fraction radiosurgery (SRS) using either multi-headed cobalt unit (Gamma Knife - GKSRS) or a linear accelerator (Linac SRS), or as stereotactic conformal radiotherapy (FSRT) delivered as fractionated treatment using a linear accelerator. The principal advances of stereotactic compared to conventional irradiation are improved immobilisation using either fixed or relocatable frames and improved image co registration and 3D planning using an external fiducial system as developed for stereotactic neurosurgery.
Large series assessing the long term effectiveness of CRT report a local control in the region of 80%-90% at 10 years and 75%-90% at 20 years. Most studies of conventional RT report normalization of GH/IGF-I levels in 30-50% of acromegalic patients at 5-10 years and 75% of patients at 15 years after treatment. GH levels fall to around 50% by 2 years with IGF-1 taking longer. Lower initial levels are associated with faster biochemical control of the disease. The toxicity of conventional RT is low, with a reported incidence of optic neuropathy resulting in visual deficit of 1-3%, and risk of necrosis of normal brain structures of 0-2%. Hypopituitarism represents the most commonly reported late complication of radiotherapy, occurring in 30-60 % of irradiated 10 years after treatment and the proportion is likely to increase with time. An increased incidence of cerebrovascular accidents and second tumors have been reported in patients with pituitary adenoma treated with conventional RT, although the relative contribution of radiation to its frequency remains to be determined.
SRS data for patients with acromegaly have been reported in more than 30 studies with a 5-year control rate in the region of 90% and a variable biochemical control of disease of 40-60% at 5 years. Hypopituitarism have been reported in 6-41%, with an incidence of visual deficits in 0-7% of patients. FSRT data for patients with either non-functioning or secreting pituitary adenomas show a tumor control in 95% of patients at 5 years, although there is limited data on FSRT in patients with secreting pituitary tumors. Normalization of elevated GH level is reported in 50-70% of patients at 5 years. In a small series of 12 patients, control of elevated cortisol concentration was reported in nine out of twelve patients (75%) at a median time of 29 months. Hypopituitarism was reported in 20% of patients; other late complications were rarely recorded.
In conclusion, RT remains an effective treatment in patients with GH-secreting pituitary adenomas not cured by surgery or medical therapy achieving excellent rate of long term tumor control. A single fraction treatment may represent a convenient approach for patients with small pituitary adenomas well away from the optic chiasm. SRS can not be recommended as the treatment of adenomas closely to optic chiasm and/or larger than 2.5-305 cm in size.

ROUND TABLE
REVIEW ON SURGERY OF GASTRO-ENTERO - PANCREATIC AND TORACIC NEUROENDOCRINE- TUMORS

The experience of Policlinico Universitario A. Gemelli
Chairmen: **A. Bianchi, A. Fabbri, C. P. Lombardi**

Sergio Alfieri
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"Outcome of pancreatic surgery in PAN-NET"

Purpose
Few data are available regarding robotic distal pancreatectomy(RDP) for pancreatic neuroendocrine tumors(pNETs) treatment. Our aim is to present the results of a multicenter study on the perioperative and long-term outcomes after RDP for pNETs.

Methods
All RDPs for pNETs performed in 4 referral centers from 2008 to 2016 were included. Perioperative outcomes, histopathological results, overall and disease-free survival were evaluated.

Results
Ninety-six patients were included. Spleen preservation was performed in 64 cases(65.3%).
Operative time was 270.2(±90.2)minutes. An intraoperative ultrasound study was required in 35 patients. Conversion rate was 9.4%. Morbidity occurred in 45 cases(46.9%), mainly due to grade A fistulas. Reoperation was needed in 6 patients. Postoperatively, one patient died of sepsis due to a grade C fistula. Hospital readmission was required in 11 cases. Sixty-eight lesions were nonfunctional and 27 lesions were functional whereas an ectopic spleen was detected in one patient. A R0 resection was always achieved. The number of harvested lymph nodes was 11.2(±13.75). Mean follow-up was 44(±26.3)months. Five-year overall and disease-free survival were 97% and 91% respectively.

Conclusions
RDP for the treatment of pNETs reached perioperative outcomes comparable to the laparoscopic approach. However, additional benefits were noted in terms spleen preservation rate and long-term survival.

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"Non-small cell lung cancer with chest wall involvement: integrated treatment or surgery alone?"

Background
The aim of this study was to identify prognostic factors in patients affected by non-small cell lung cancer (NSCLC) with chest wall (CW) involvement, analyzing different strategies of treatment and surgical approaches.

Methods
Records of 59 patients affected by NSCLC with CW involvement underwent surgery were retrospectively reviewed, from January 2000 to March 2013.

Results
Induction therapy was administered to 18 (30.5%) patients while adjuvant treatment to 36 (61.0%). In 36 (61%) patients, lung resection was associated only with a parietal pleural resection while in 23 (39%) with CW en-bloc resection. Overall 5-year survival was 34%. Prognostic factors were evaluated in the 51 (86.4%) completely resected (R0) patients. Five-year survival was 60% in patients undergoing induction therapy followed by surgery and 24%inthosewhounderwentsurgeryasfirst treatment (p ¼ 0.11).Five-year survivalwasbetter in the neoadjuvant group than that in the surgery group in IIB (T3N0) p-stage (100 vs 28%, p ¼ 0.03), while in the IIIA (T3N1–2,T4N0)p-stageitwas of 25vs 0%, respectively (p ¼ 0.53). No 5-year survival difference was found in case of parietal pleural resection versus CW en-bloc resection (p ¼ 0.27) and in case of only parietal pleural involvement versus soft tissue (p ¼ 0.78).
In case of incomplete resection (R1), patients undergoing adjuvant radiotherapy had better 2-year survival than patients untreated: 60% vs 0% (p ¼ 0.025).
Conclusions Type of surgical resection and the deep of infiltration of disease do not influence survival in this subset of patients. Integrated treatments seem to be suitable: neoadjuvant therapies ensure a better survival rate than surgery alone in IIB and IIIApatients, instead adjuvant radiotherapy proves a fundamental option in incomplete resections.

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"Endocrine surgeon in the management of patient affected by MEN1"

The role of the endocrine surgeon in the treatment of patients affected by multiple endocrine neoplasia type I (MEN1) has to be searched in the surgical management of pancreatic tumors, primary hyperparathyroidism (PHPT) and adrenal diseases that variably manifest in MEN1 patients.
Pancreatic tumors in MEN1 will be addressed in another talks.
PHPT is the most common manifestation and should be treated first, particularly in patients with Zollinger-Ellison Syndrome, since hypercalcemia simulates gastrin secretion. PHPT is the first clinical manifestation in 90% of carriers. The typical presentation is at age of 20-25 years and approximately 90% of the carriers present the disease by the age of 50 years. Due to genetic mutation, the disease is characterized by a multigland disease, which is often asymmetric, and is associated with increased incidence of supernumerary glands. The surgical aim is to remove as much as hyperplastic parathyroid tissue leaving a small fragment that could reduce the risk of permanent hypoparathyroidism, while avoiding at the same time the risk of persistent and/or recurrent disease. In most Institution the operation of choice is a subtotal parathyroidectomy leaving a well vascularized remnant marked with either clip or a prolene suture or both – away from the recurrent laryngeal nerve. Total parathyroidectomy with heterotopic autotransplantation is another possible option. Cryopreservation should be considered. The risk of remedial cervical exploration is greater with the former strategy, while the risk of hypoparathyroidism is greater with the latter. A thorough search for supernumerary and ectopic glands should be performed. Thus, thymectomy should be part of the operation since it removes occult parathyroid glands and helps prevent development of thymic carcinoid tumors. Minimally invasive video-assisted bilateral exploration and subtotal parathyroidectomy may be an option in selected cases.

Thirty-five to forty percent of MEN 1 patients harbor adrenocortical lesions, and these are clearly overrepresented in the MEN 1 syndrome. The majority of lesions are hyperplastic, bilateral, and nonfunctioning. Aldosterone- and cortisol-secreting adenomas, however, have been reported. Hypercortisolism in MEN 1 can be the result of an ACTH-secreting pituitary adenoma, a cortisol-secreting adenoma/carcinoma, or, very rarely, due to an ACTH or corticotropin releasing hormone-producing islet cell tumor or thymic carcinoid. Adrenocortical carcinomas have also been described in MEN 1 patients, most often in association with insulin-producing islet cell tumors. Patients should be offered yearly screening examination with resection criteria similar to that of patients with sporadic disease. Patients with functioning unilateral lesions should undergo unilateral adrenalectomy.

Laparoscopic adrenalectomy, both via the transperitoneal lateral and the retroperitoneoscopic approach, has to be considered as the procedure of choice for small to medium size benign lesions. Larger and potentially malignant lesion should be better approached by a conventional open approach, despite laparoscopic exploration can be offered in selected cases as a first step. Patients with ACTH-dependent Cushing's syndrome, when refractory to primary tumor resection and to medical treatment, should be selected for bilateral endoscopic adrenalectomy. Simultaneous bilateral posterior retroperitoneoscopic approach offer significant advantages in terms of reduction of operative time and operative stress.

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"Surgical treatment of gastroduodenal neuroendocrine neoplasms"

Gastroduodenal neuroendocrine tumors are rare neoplasms. Gastric neuroendocrine tumors (G-NETs) have a reported incidence of 0,16 per 100000 and a prevalence of 3,4 per 100000 people in Europe, and duodenal NETs (D-NETs) are even rarer, with a reported incidence of 0,19 per 100000 in the United States and a prevalence of 0,4-0,17 per 100000 people in Europe and Japan. In the last years, a significant increase in the incidence of gastric and duodenal neuroendocrine tumors have been reported. G-NETs are classified into three subtypes. Type I G-NETs are the most common subtype (70%-80%). They are associated with chronic atrophic gastritis (autoimmune gastritis and Helicobacter pylori associated atrophic gastritis). Type II G-NETs (5%-6%) are associated with multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome (MEN1-ZES). Both type I and II G-NETs are related to hypergastrinemia, are small in size, occur in multiple numbers, and are generally benign. Type III G-NETs (10%-15%) are single, sporadic, not associated with hypergastrinemia, and are usually malignant and aggressive. Given the relatively benign nature of type I and II G-NETs and their low local aggressiveness and metastatic potential, these tumors are usually well-managed by endoscopic resection and follow-up. Surgery has a role in non-initial tumors and recurrent type-I G-NETs. Instead, in patients with type III G-NETs, surgical resection and platinum-based chemotherapy are generally necessary, while endoscopic resection is acceptable only for small and well differentiated type III G-NETs. D-NETs are rarer than G-NETs. D-NETs include five histological types: gastrinomas (50-60%), somatostatin-producing tumors (15%), nonfunctional serotonin-containing tumors (20%), poorly differentiated neuroendocrine carcinomas (< 3%), and gangliocytic paragangliomas (< 2%). Most D-NETs are located in the first or second part of the duodenum, with 20% occurring in the periampullary region. Their therapy is based on tumor location, grade, stage, and size. While endoscopic resection may be considered for well-differentiated, small, nonfunctional D-NETs located in the higher papilla region, surgical resection is necessary for most other D-NETs. In the setting of metastatic disease, both for G-NETs and D-NETs, the role for surgery has to be carefully weighted and individualized.