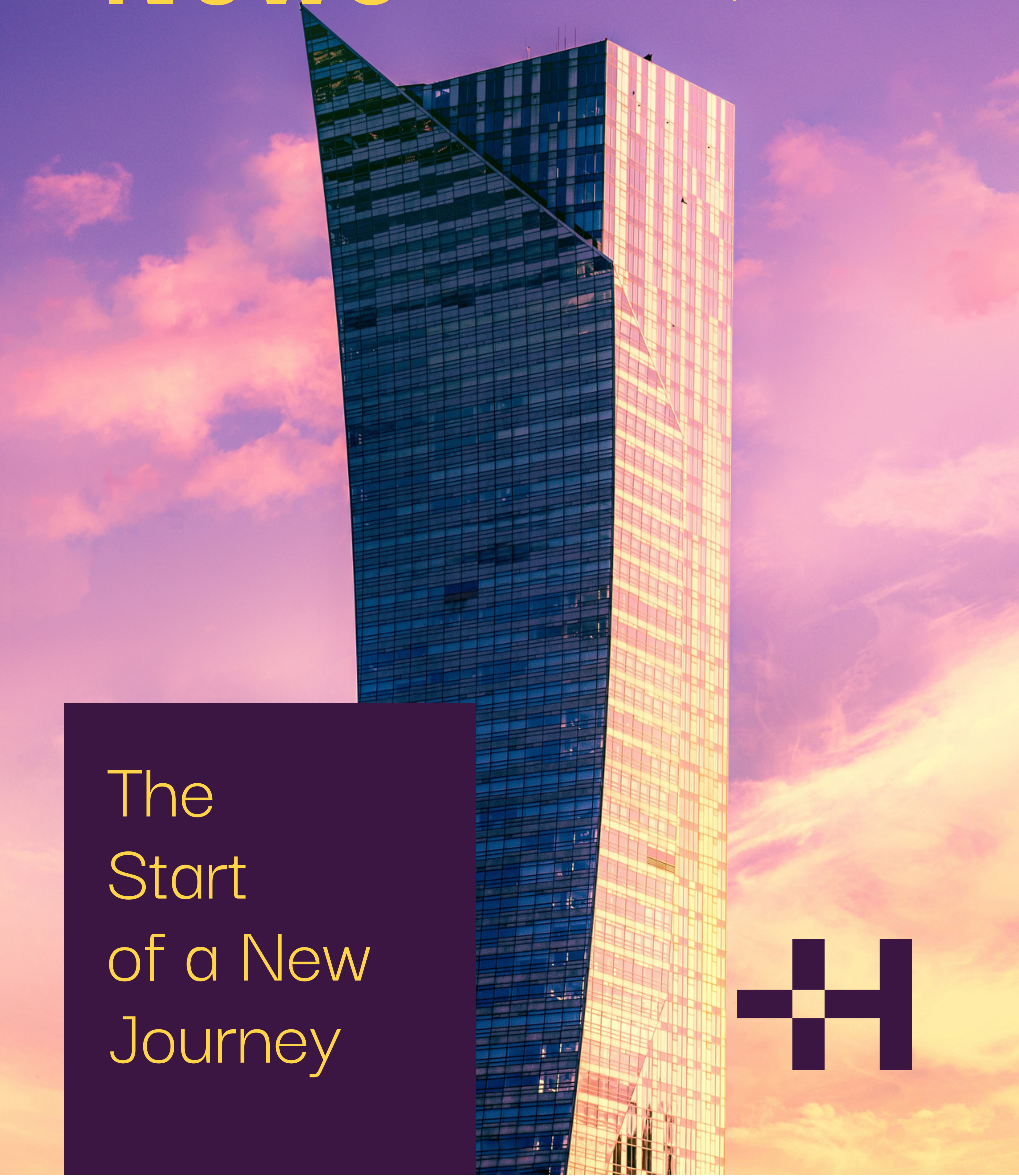
The Official Newsletter of the COST Action CA20122

Harmonis@tion News

Issue No 1
September 2022



The Start of a New Journey

In this issue

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Welcome note from Editorial Board

The adrenal tumour research community is buzzing with activity!
Our field clearly sets an example that rarity of disease can not be an excuse not to perform science with the highest quality. Many colleagues ask how this can be possible? Among us are many excellent minds. But what distinguishes the adrenal tumour field is our strong network with collaborative spirits. And hard work.
With three yearly issues the Harmonis@tion Newsletter will try to weave everything together, presenting you with the latest updates from the
COST Action CA20122.

We hope you enjoy it!

Joakim Crona

Funded by the Horizon 2020 Framework Programme of the European Union

AI dictionary for researchers and clinicians

Traditionally, medical institutions have been dealing with large amounts of paperwork. Every clinic patient has a medical record that includes results of various screenings and radiology images describing patients' medical history. The development of information technology and computing led to the migration of that medical data to a digital format. The digital format allows for easier statistical analysis and easier acquisition of large datasets, which are critical aspects of modern Artificial Intelligence (AI) systems. Formally, AI is viewed as the field of study of intelligent agents. In modern information systems, those agents are mathematical algorithms running on digital hardware. As such, AI is used as an umbrella term for many different applications and algorithms. Those algorithms take data as input and make decisions or estimations based on previously gathered information. The quality of those decisions and estimations is evaluated by the criteria defined by the designer of the system. How knowledge is gathered and represented is the primary way to differentiate AI systems.

Machine learning (ML) is a branch of AI that studies algorithms that observe input data, build a model based on the data, and use the model as both a hypothesis about the world and a piece of software that can solve problems. ML systems learn by induction, as they start from a specific set of observations and find general rules.

Training is a process where an algorithm observes the input data and creates a map between input and output.

Pattern recognition is a type of ML problem where the possible output is a finite set of values. It is also called classification, as output values are groups into which the input observations are mapped. Some examples of classification would include prediction of outcomes in gastrointestinal bleeding, diagnosis of gastroesophageal reflux disease, early detection of atrial fibrillation, etc.

Regression is a type of ML problem where the possible output is a numeric value. A more descriptive name would be function approximation or numeric prediction, but the term regression is used due to historic reasons. Some examples of regression would include prediction of direction and rate of change of blood glucose levels, prediction of the decline of glomerular filtration rate in patients with polycystic kidney disease, prediction of the risk of cardiovascular disease, etc.

Supervised learning is a training strategy where the algorithm observes input-output pairs and learns the function that maps from input to output. For example, the inputs could be radiology scans (images), each one accompanied by an output saying "benign tumor", "malign tumor" or "healthy tissue". A more descriptive name would be function approximation or numeric prediction, but the term regression is used due to historic reasons. Some examples of regression would include prediction of direction and rate of change of blood glucose levels, prediction of the decline of glomerular filtration rate in patients with polycystic kidney disease, prediction of the risk of cardiovascular disease, etc.

Unsupervised learning is a training strategy where the algorithm learns patterns in the input data set without any explicit output label or measurement. The most common unsupervised learning task is clustering - detecting potentially useful patterns and correlations in input examples.
Reinforcement learning is a training strategy where the algorithm learns from a series of reinforcements: rewards and punishments. For example, at the end of a chess game, the agent is told that it has won (a reward) or lost (a punishment). It is up to the agent to decide which of the actions prior to the reinforcement were most responsible for it and to alter its actions to achieve more rewards in the future. [2]
Deep learning is a broad family of techniques for machine learning in which models take the form of complex algebraic circuits with optimizable connection strengths. The word "deep" refers to the fact that the circuits are typically organized into many layers, which means that computation paths from inputs to outputs have many steps. Deep learning is currently the most widely used approach for applications such as visual object recognition, machine translation, speech recognition, speech synthesis, and image synthesis; it also plays a significant role in reinforcement learning applications. Deep learning has its origins in early work that tried to model networks of neurons in the brain (McCulloch and Pitts, 1943) with computational circuits. For this reason, the networks trained by deep learning methods are often called neural networks, even though the resemblance to real neural cells and structures is superficial. [2]
Data mining is the process of extracting useful information from a large collection of data that was previously unknown. It is a broad term, which includes techniques from AI, ML, statistics and database systems. Some examples of data mining are assessment of effectiveness of treatment, healthcare management and improvement of patient care.
Computer vision (CV) is a branch of AI that develops algorithms for automatic extraction, analysis and understanding of useful information in a single image or a video. An example CV would be image processing for the detection of abnormal structures such as colonic polyps.
Natural language processing (NLP) is a branch of AI that develops algorithms that can use natural language to communicate with humans and learn from what they have written. [2] An example of NLP would be extraction of information from textual medical records.
Overall, AI is a dynamic field where new algorithms and techniques are constantly being developed. Because of that, one may find it hard to navigate its ever changing landscape. Good understanding of the basic concepts can significantly ease the use of new algorithms and concepts.

References:

[1] Giovanni Briganti, Olivier Le Moine. Artificial Intelligence in Medicine: Today and Tomorrow. Frontiers in Medicine, 05 February 2020

[2] Stuart Russell, Peter Norvig. "Artificial intelligence, A Modern Approach", Fourth Edition. Prentice Hall (2020)

[3] Umar Sidiq, Dr.Rafi Ahmad Khan. "Data Mining for diagnosis in Healthcare Sector-A Review", International Journal of Advances in Scientific Research and Engineering, E-ISSN 2454-8006

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Why join Harmonis@tion?

The European Cooperation in Science and Technology (COST) is an EU-funded programme that enables researchers to set up their interdisciplinary network to study some relevant topics. In this context, and with the aim to harmonise clinical care and research on adrenal tumours, which is quite heterogeneous across European countries, we constituted a pan-European multidisciplinary collaborative network called HARMONISA@TION. Besides clinicians and researchers, this network also consists of experts in information technology, artificial intelligence, databases, data protection as well as experts in the legal and ethical field. We strongly believe that such a multidisciplinary and geographically widespread network will generate strong synergisms.
HARMONIS@TION promotes the highest standards in clinical management of adrenal tumours and bridges the fields of medical research, information technology, and ethics/regulations. It facilitates international collaboration, enables breakthrough scientific developments and strengthens European research and innovation capacity.

”Harmonis@tion fosters creation and exchange of knowledge and enables the development of a joint research agenda on adrenal tumours at the European level”

HARMONIS@TION activities are organised in five Working Groups: 1. Harmonising clinical practice of adrenal tumours; 2. Harmonising adrenal tumour research and -omics practice; 3. Harmonising Information Technology (IT)/Artificial Intelligence (AI) tools towards a standardised registry; 4. Harmonising the ethical and legal framework required for federated European trials; and 5. Communication, dissemination, and inclusiveness.
One of the cornerstones of HARMONIS@TION is to include early career clinicians and researchers in all its activities. They will be specifically targeted through master classes and training schools, short-term scientific missions, workshops, and conferences. This will promote their careers by helping them acquire new skills and build/expand their international networks.
HARMONIS@TION fosters creation and exchange of knowledge and enables the development of a joint research agenda on adrenal tumours at the European level. Furthermore, it offers an inclusive, pan-European environment for individuals of all levels of seniority to grow their research networks, and finally, it enables each individual to boost their personal professional growth.
For all these reasons, we cordially invite you to join the Action and we hope to see you at one of the upcoming HARMONIS@TION meetings.

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The joint 21st ens@t and 1st COST-Harmonis@tion meeting

28 – 30 Sept 2022, Warsaw, Poland

Following the very successful 1st Adrenal Tumor Master Class, which took place as an online seminar in March 2022, the second occasion is set out to take place on site at Warsaw, Poland in conjunction with the yearly ENS@T scientific meeting on September 28th, 2022.
We are very fortunate to have both experienced speakers as well as energetic young colleagues that will cover a broad range of clinical and scientific aspects of adrenal tumors.
The clinical sessions will be equally distributed among the four traditional ENS@T categories as adrenocortical cancer, pheochromocytoma/paraganglioma, non-aldosterone adrenocortical adenomas (such as incidentalomas and cortisol-producing adenomas) and aldosterone producing adenomas/ primary aldosteronism. While the junior colleagues will present typical or enigmatic cases or those that highlight clinical problems the senior partner will provide a targeted overview on the current state-of-the-art procedures and therapies.
For the scientific part an expert in computational methods will review concepts and tools needed to manage omic patient data and bring us a little closer to personalized medicine. Another relevant aspect that will be discussed will be the importance of the implementation of artificial intelligence in the clinical setting. Both fields of study have proven to be robust tools at the service of accurate diagnosis and increasingly individualized treatment.
The interaction between clinicians, basic researchers and professionals from other disciplines such as bioinformaticians or mathematicians in the same event will undoubtedly be an enriching experience, and will give the opportunity to take the first steps towards harmonization in the management and study of patients with adrenal tumors in Europe.
The overarching purpose of this masterclass is to improve and foster knowledge in the broader area of adrenal tumors and related diseases throughout Europe (and beyond).

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PUBLICATION SPOTLIGHT

Otilia Kimpel:

Adjuvant platinum-based chemotherapy in radically resected adrenocortical carcinoma: a cohort study

Harmonization had the pleasure to speak to Otilia Kimpel, based at the University Hospital in Würzburg, Germany. She is currently in her fourth year of residency, specializing in endocrinology and diabetes, but already has already experience from treating patients and doing research on adrenocortical carcinoma (ACC). Otilia is enthusiastic about her work and highlights the fantastic academic environment at her center. She is enrolled in the clinician scientist program under the supervision of Prof. Stefanie Hahner and Prof. Martin Fassnacht: her aim is to focus on ACC that has very limited therapeutic options and a high rate of recurrence even after complete resection. Therefore, they have decided to study the potential of adjuvant treatments. In other solid malignancies, the use of adjuvant cytotoxic chemotherapy is known to reduce the risk of disease recurrence. However, the role of adjuvant chemotherapy in ACC has not been established, and the available evidence is extremely limited. According to the ESE and ESMO guidelines, adjuvant platinum-based chemotherapy should be considered in selected patients with very high risk for recurrence. As there is no data available from randomized trials, they decided to study retrospective data available at different ACC centers. This cohort study was announced as an ENSAT project using the ENSAT registry (www.ensat.org/registry) and four European reference centers for ACC (Würzburg, Germany; Brescia, Italy; Berlin, Germany; and Orbassano, Italy) and the MD Anderson Cancer Center in Houston, US, participated. Their aim was to investigate the efficacy of adjuvant platinum-based chemotherapy in patients with very high-risk of recurrence.

In their study they screened for ACC patients that have had adjuvant platinum-based chemotherapy. Furthermore, a control group without an adjuvant chemotherapy was collected. In total, 299 patients were screened, 31 of whom have been treated with an adjuvant platinum-based therapy. This unique material was studied using two different methodological approaches: First, every patient was matched with one control patient according to the following criteria: Ki67 index (+/- 5% in tumors with Ki67 <20%, +/-15% in tumors with Ki67 20-49% and +/-20% in tumors with Ki67 ⩾50%) resection status (R0, R1, Rx), tumor stage, concomitant treatment with mitotane (yes/no), and presence of preoperative glucocorticoid excess (yes/no). To reduce the impact of potential immortal time bias, they performed a landmark analysis excluding all patients who experienced recurrent disease or died within 12 weeks after radical resection. Secondly, a propensity score approach was applied and used in a multivariable model.

The results of this study were clearly in favor of adjuvant platinum chemotherapy. Patients with adjuvant platinum-based therapy had a longer median recurrence free survival than matched controls (20.5 months vs. 9.1 months; p<0.001). In a multivariable analysis adjusted hazard ratio for recurrence free survival was of 0.35 (95% confidence interval 0.19-0.67;p=0.001). After adjustment for propensity scores and accounting for immortal time bias, the hazard ratio for recurrence free survival was 0.45 (95% confidence interval 0.29-0.89, p=0.021).
Otilia and colleagues concluded that adjuvant platinum-based chemotherapy was associated with beneficial effects on clinical outcome in this high-risk group of patients with adrenocortical carcinoma.
While performing her first study in the field of ACC Otilia was trained in various research methodologies including different statistical analyses and also got to deal with publication issues. Another advantage with working hands on was to get in contact with other ACC centers and to develop international collaborations which will be of great value for future projects. Otilia already has further plans and wishes to look for individual differences which could predict the response to an adjuvant platinum-based chemotherapy. Therefore, she is working on a project that is doing 3 RNA sequencing. She also aims to help in proving the value of this therapy in a randomized prospective study. And such a trial is now running: ADIUVO-2 and we hope that many centers will contribute to this important study.

Joakim Crona, Liang Zhang & Kazhan Mollazadegan

Let's Cure ACC - Patient group

is an international patient advocacy non-profit association focusing on Adrenocortical Carcinoma (ACC) considering the rarity of the disease, the few medical experts worldwide and the difficulties to diagnose it for a non-medical expert.
Our goals are to:
- Give basic and understandable information about the disease and all related data to patients in multiple languages to promote self-learning for patients
- Be a reference by listing all resources available: comprehensible medical resources, websites, patients' groups
- Offer a "human" understanding of the disease through stories of survivors, and families of "lost" ones
- Create a bridge between patients and ACC medical experts by:
  - providing a list of medical resources (medical specialists, centers, ...) by country/language
  - offering the most understandable medical papers understandable for non-medical persons,
  - help for trials
- Be a valuable resource for all medical experts, groups and associations worldwide (ENSAT-Europe, NIH-USA) to help in the fight for the recognition of the disease, raise awareness and for a better cure of ACC.

Anja Barač Nekić

Recognized by: COMET (France), NIH My Part/Cancer.gov (USA)
https://www.cancer.gov/pediatric-adult-rare-tumor/participate/partners

LATEST RESEARCH

Development of [18F]AldoView as the First Highly Selective Aldosterone Synthase PET Tracer for Imaging of Primary Hyperaldosteronism

The authors of this article sought to develop a selective PET-tracer for increased aldosterone synthase (CYP11B2) activity, leading to the denoted tracer [18F]AldoView. Immunohistochemical staining for CYP11B2 was in concordance with high uptake areas of aldosterone producing adenomas, in resected adrenal glands of primary hyperaldosteronism patients. Aldosterone producing cell clusters in the cortex had "hot spots" compared to the rest of the cortex. No tracer uptake was seen in CYP11B2-negative control subjects and in negative areas of primary hyperaldosteronism patients specimens. The authors conclude that in vivo imaging could be attainable with [18F]AldoView.

Sander, K. et al. (2021). Development of [18F]AldoView as the First Highly Selective Aldosterone Synthase PET Tracer for Imaging of Primary Hyperaldosteronism. Journal of medicinal chemistry, 64(13), 9321–9329. https://doi.org/10.1021/acs.jmedchem.1c00539

Machine Learning-Based Texture Analysis in the Characterization of Cortisol Secreting vs. Non-Secreting Adrenocortical Incidentalomas in CT Scan

The authors sought to distinguish functional Adrenal incidentalomas (AIs) from non-functional AIs using a machine learning-based computed tomography texture analysis. 314 radiomics characters were extracted from 72 AIs (32 secreting and 40 non-secreting masses). A predictive model consisting of eleven variables were then scored for each patient. The model showed a sensitivity of 93.75% and a specificity of 100% in differentiating functional AIs. Authors concluded that CT texture analysis could be a promising tool in the diagnostic definition of AIs.

Maggio, R. et al. (2022). Machine Learning-Based Texture Analysis in the Characterization of Cortisol Secreting vs. Non-Secreting Adrenocortical Incidentalomas in CT Scan. Frontiers in endocrinology, 13, 873189

Determinants of disease-specific survival in patients with and without metastatic pheochromocytoma and paraganglioma

The authors sought to explore predictors of disease-specific survival (DSS) in pheochromocytomas/paragangliomas (PPGLs) and head/neck paragangliomas (HNPGLs). Data from 582 patients with PPGLs and 57 with HNPGLs were analyzed. In all PPGLs, shorter DSS was associated with older age, presence of metastases, extra-adrenal tumor location, higher plasma methoxytyramine and normetanephrine. Among patients with HNPGLs, only plasma methoxytyramine was an independent predictor of DSS. In metastatic PPGLs, older age, elevated plasma methoxytyramine, the presence of synchronous metastases and extensive metastatic burden were independent predictors of shorter DSS.

Pamporaki, C. et al. (2022). Determinants of disease-specific survival in patients with and without metastatic pheochromocytoma and paraganglioma. European journal of cancer (Oxford, England : 1990), 169, 32–41.

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cost EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

Funded by the Horizon 2020 Framework Programme of the European Union