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[1] Guillaumier et al. Eur Urol. 2018; 74(4):422-429

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暨聯合學術研討會

1

精準醫療在兒科的新進展暨國科會兒科學門研究成果發表

Advancement of Precision Medicine and Achievement Presentation in the Discipline of Pediatric Medicine of Ministry of Science and Technology

時 間：112年7月8日 08:00~17:30

Time：July 8, 2023 08:00~17:30

地 點：臺北榮民總醫院 致德樓第一會議室

Place：The First Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

精準醫療在兒科的新進展暨國科會兒科學門研究成果發表
Advancement of Precision Medicine and Achievement Presentation in the Discipline of Pediatric Medicine of Ministry of Science and Technology

Gut dysbiosis on pediatric health and diseases

菌相失衡對兒童疾病之影響

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Gut microbiota signatures acquired in infancy may predict the future development of diseases. The gut microbiota modulate the development of immune, metabolic, neurologic and psychiatric systems, and may impact some diseases course through their metabolic pathways. The diseases involved, such as metabolic diseases, cancers, immunologic diseases, and neurologic disorders, may be attributed to the dysbiosis in the early life. Many factors affect the constitutions of the gut microbiota, including maternal nutrition, delivery routes, diet, geography, genetic factors, age, and drugs, and antibiotics. The diversity of the gut microbiota is one of the measures to define “dysbiosis”. Proteobacteria, Actinobacteria, Bacteroidetes, and Firmicutes are the major bacterial phyla in infancy. The infants’ gut microbiota pattern gradually transit into the adult pattern around the age of three, when the food intake of the children is similar to that of the adults. A long-term prospective monitoring on the development of diseases and the evolution of gut microbiota will be very helpful to unravel their critical role in the pathogenesis of many diseases and the gut microbiota may become the therapeutic target. We have already proven an early colonization with R. gnavus in the gut promoted allergic disease in infants. We also demonstrated that Desulfovibrio could induce non-alcoholic liver diseases in obese children. The concept may be applied to many immune-related conditions. The current focus of microbiota studies is on their metabolites, which are produced by the host-microbiota interaction and then affect many organs and diseases of the hosts. A long-term prospective monitoring on the development of diseases and the evolution of gut microbiota will be very helpful to unravel their roles in pediatric diseases. In the meantime, the responsible gut microbiota and their gene products/metabolites may become the therapeutic target(s).

Microbiota regulate social behaviour via stress response neurons in the brain

微生物群落透過大腦中的壓力反應神經元調節社會行為

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Social interactions among animals mediate essential behaviours, including mating, nurturing, and defence1,2. The gut microbiota contribute to social activity in mice3,4, but the gut–brain connections that regulate this complex behaviour and its underlying neural basis are unclear5,6. Here we show that the microbiome modulates neuronal activity in specific brain regions of male mice to regulate canonical stress responses and social behaviours. Social deviation in germ-free and antibiotic-treated mice is associated with elevated levels of the stress hormone corticosterone, which is primarily produced by activation of the hypothalamus–pituitary–adrenal (HPA) axis. Adrenalectomy, antagonism of glucocorticoid receptors, or pharmacological inhibition of corticosterone synthesis effectively corrects social deficits following microbiome depletion. Genetic ablation of glucocorticoid receptors in specific brain regions or chemogenetic inactivation of neurons in the paraventricular nucleus of the hypothalamus that produce corticotrophin-releasing hormone (CRH) reverse social impairments in antibiotic-treated mice. Conversely, specific activation of CRH-expressing neurons in the paraventricular nucleus induces social deficits in mice with a normal microbiome. Via microbiome profiling and in vivo selection, we identify a bacterial species, Enterococcus faecalis, that promotes social activity and reduces corticosterone levels in mice following social stress. These studies suggest that specific gut bacteria can restrain the activation of the HPA axis, and show that the microbiome can affect social behaviours through discrete neuronal circuits that mediate stress responses in the brain.

Trained immunity and immune metabolism of macrophages in allergic disorders

訓練免疫和巨噬細胞免疫代謝在過敏性疾病中的作用

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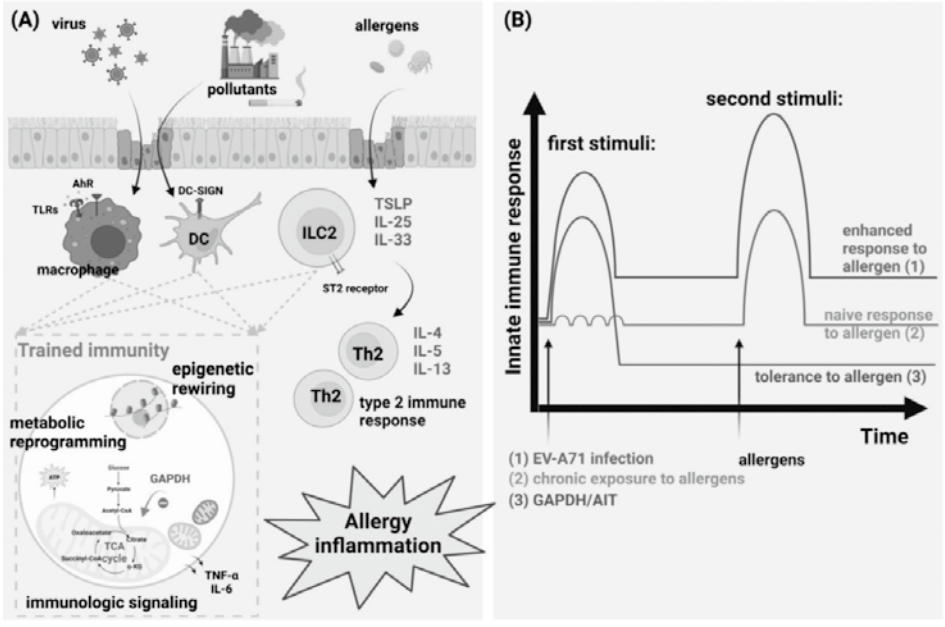
Early-life exposure to environmental allergens and viral infections can lead to trained immunity and macrophage polarization resulting in an augmented type 2 immune response in allergic disorders. However, the detailed mechanism is unknown. We found that early-life enterovirus (EV-A71) infection was correlated with an increased risk of allergic diseases in children, and resulted in increased allergen-induced airway inflammation in experimental asthma in EV-infected mice. Furthermore, we found that trained macrophages were crucial in the progression of allergic asthma

later in life after enterovirus infection [Chen PC, et al. Early-life EV-A71 infection augments allergen-induced airway inflammation in asthma through trained immunity of macrophages. Cell Mol Immunol. 2021;18:472–83.]. This is the first report that confirmed that trained immunity is involved in the development of allergic asthma, and provides a new and rational preventive or treatment modality for allergic disorders in the airways. In this invited speech, I will focus on the mechanism of innate immune response and trained immunity in allergic diseases (summarized in the figure of Cell Mol Immunol, 2023, Apr 4. doi: 10.1038/s41423-023-01005-0.).



New advance in juvenile dermatomyositis

皮肌炎的新進展

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Juvenile dermatomyositis (JDM) is a symmetrical inflammatory myositis predominantly affecting proximal muscles with characteristic skin lesions. However, some cases lack muscle weakness despite skin lesions characteristic of JDM and this is currently called juvenile clinically amyopathic dermatomyositis (JCADM). JDM-related polymorphisms are reported in the genes encoding TNF-α promotor, interleukin-1β, interleukin-1 receptor antagonist intron, interferon regulatory factor 5 (IRF5), mannose-binding lectin (MBL), chemokine (C-C motif) ligand 21 (CCL21), phospholipase C-like protein a (PLCL1) and B lymphoid kinase (BLK). Reported environmental factors include infectious agents such as coxsackievirus, influenza virus, parvovirus, hepatitis B virus, group A streptococcus, toxoplasma, and borrelia, as well as vaccines, ultraviolet exposure, and medications. Histopathological studies have revealed ischemic change due to inflammatory or non-inflammatory systemic vasculopathy, and both apoptosis of the muscle cells and amplification of inflammation mediated by type-I interferon (IFN). Recently established both MRI and myositis-specific autoantibodies (MSAs) instead of electromyography and anti-Jo-1 antibodies, respectively. Butterfly erythema which spreads over the cheeks on both sides of the root of the nose and often over the entire face is frequently an initial dermatological symptom of JDM. Periungual erythema is not specific but often observed as an initial symptom of JDM. Calcinosis is a characteristic cutaneous sign in JDM. Undermining ulcer is a possibly vasculitis-associated ulcerative lesion expanding from the dermis into subcutaneous tissues and associated with anti-MDA5 autoantibodies. Calcinosis is observed in 30–70% of patients with JDM and associated with prolonged disease activity due to delay in diagnosis or commencement of treatment, cardiac involvement, and anti-NXP2 autoantibodies. Surgical treatment is often necessary but should not be performed when disease is active. Thrombocytopenia with or without cytopenia of other lineages has been reported. Effectiveness of GC, immunosuppressants, and IVIG has been reported. Arrhythmias or myocarditis/cardiomyopathy is rare, recent studies have demonstrated subclinical cardiac dysfunction in late disease which is associated with sustained early skin disease rather than myopathy.

The current clinical applications of whole genome sequencing

全基因體定序在臨床上應用的現況

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The rapid progress in deciphering the human genome and advancements in next-generation gene sequencing technology have made whole genome sequencing (WGS) more affordable and accessible to a broader population. However, the efficient processing and analysis of the vast amount of data generated by WGS pose a significant challenge. In response, our center has collaborated with a bioinformatics service company to develop a "rapid real-time WGS analysis system" that combines gene analysis technology, cloud computing, big data, and artificial intelligence. Our primary objective is to enable swift and accurate diagnosis for patients with genetic diseases through this innovative analysis system. In this talk, we will present compelling cases of inherited diseases to illustrate the operational capabilities of our analysis system. Moreover, our collaborative efforts have resulted in the creation of "strata finder," a specialized AI algorithm embedded within the genomic AI analysis system. This algorithm utilizes patient WGS data to assess the risk of complex diseases, such as asthma, acute myocardial infarction (AMI), and stroke. Our preliminary data shows that strata finder achieves accuracy rates of 96% or higher. The rapid real-time analysis system also encompasses additional features, including pharmacogenomics analysis, constitution analysis, proactive analysis, HLA typing analysis, and more, thereby providing clinicians with comprehensive and precise patient information. A key focus during the development process has been the creation of a concise, user-friendly interface for the genetic analysis system, ensuring ease of use and understanding. Our ultimate goal is to make WGS analysis more accessible and usable for general physicians, thereby driving the advancement of precision medicine in Taiwan. By facilitating early intervention and personalized treatment strategies based on genetic insights, we aspire to realize the concept of "prevention is better than treatment" in public healthcare.

Genetic testing for pediatric neurological disorders

基因檢測於兒童神經疾患

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Pediatric neurological disorders consist of a group of diverse diseases, ranging from common disorders such as developmental delay (DD)/ intellectual disability (ID), autism spectrum disorder (ASD), and epilepsies, to rare diseases like neuromuscular, neurometabolic, neurodegenerative disorders and many more. The underlying etiologies of these disease entities vary widely, and genetic factors play a pivotal role. Therefore, genetic and genomic testing have become the backbone of diagnosis.

Traditional methods routinely employ clinical features, diagnostic criteria, and/or specialized biochemical tests to conduct various genetic testing, including G-banded karyotyping, fluorescence in situ hybridization (FISH), multiplex ligation-dependent probe amplification (MLPA), chromosomal microarray analysis (CMA), and/or targeted single-gene or gene-panel sequencing. Advances in bioinformatics and genomic technologies have allowed the development of whole-exome sequencing (WES) and whole-genome sequencing (WGS), and WES/WGS have been used extensively in clinical practice for increasing the diagnostic yield for this disease entity.

In this talk, I will focus on how to use these genetic testing in pediatric patients with neurological disorders.

Unlocking the secrets of early pompe disease diagnosis and treatment in Taiwan

揭開早期龐貝病診斷和治療的秘密

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Background: Starting enzyme replacement therapy (ERT) before severe irreversible muscular damage occurs is important in infantile-onset Pompe disease (IOPD). This long-term follow-up study demonstrates our diagnostic and treatment strategies for IOPD and compares our clinical outcomes with those of other medical centres.

Methods: In this long-term follow-up study, we analysed the outcomes of very early ERT with premedication hydrocortisone in patients with IOPD. Out of 1 228 539 infants screened between 1 January 2010 and 28 February 2021, 33 newborns had confirmed IOPD in Taipei Veterans General Hospital. Twenty-six were regularly treated and monitored at Taipei Veterans General Hospital. Echocardiographic parameters, biomarkers, IgG antibodies against alglucosidase alpha, pulmonary function variables and developmental status were all assessed regularly over an average follow-up duration of 6.18±3.14 years. We compared the long-term treatment outcomes of our patients with those of other research groups.

Results: The average age at ERT initiation was 9.75±3.17 days for patients with classic IOPD. The average of the latest antialglucosidase alpha IgG titre was 669.23±1159.23. All enrolled patients had normal heart sizes, motor milestones, cognitive function and pulmonary function that were near-normal to normal. Compared with patients in other studies, our patients had better outcomes in all aspects.

Conclusion: Very early ERT using our rapid diagnostic and treatment strategy enabled our patients with IOPD to have better outcomes than patients in other medical centres.

Long read whole genome sequencing analysis of rare diseases: A case study of Williams syndrome

利用長片段定序技術進行罕見疾病的全基因體序列分析：以威廉斯氏症候群為例子的研究

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Williams syndrome, also known as Williams-Beuren syndrome (WBS), is a rare genetic disorder characterized by a distinctive set of features, including cardiovascular abnormalities, cognitive impairments, and unique social and behavioral traits. The underlying cause of WBS is a microdeletion of genetic material on chromosome 7, specifically at the 7q11.23 region. This deletion affects 28 genes, including the elastin gene (ELN), which is responsible for the cardiovascular complications observed in individuals with WBS.

Though WBS is a chromosomal microdeletion syndrome, recent advancements in sequencing technologies have enabled researchers to explore the genomic landscape of WBS comprehensively. Whole genomic sequencing (WGS) has provided valuable insights into the complex genetic architecture of WBS, revealing additional genetic variations, such as copy number variants and single nucleotide variants that may modulate the clinical presentation and severity of the syndrome.

Next-generation sequencing (NGS) technologies, especially long read sequencing, offer several advantages in the study of WBS. Their ability to generate long reads enables the detection of structural variations, including the precise characterization of the size and breakpoints of the 7q11.23 microdeletion. Long reads also aid in the assembly of complex genomic regions, allowing for the identification of additional genomic rearrangements or copy number variations that may contribute to the phenotypic variability observed in WBS patients. Moreover, long read sequencing facilitates accurate haplotype phasing, which is essential for understanding the inheritance patterns and potential modifier genes in WBS. The application of long read sequencing technologies has significantly advanced our understanding of the genetic basis of WBS. Long read sequencing can aid in the precise characterization of structural variations and haplotype phasing, in addition to SNVs, and indels profiles.

In conclusion, whole genomic sequencing technologies offers a promising avenue for unraveling the complexities of WBS, facilitating personalized diagnoses, prognoses, and potential therapeutic interventions.

Neonatal hemodynamics and neurocritical care

新生兒血液動力學與神經重症監護

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Hemodynamics, which encompasses the study of blood flow, oxygen delivery, and organ/tissue consumption, is of critical importance in neonatal critical care. However, due to the physical limitations of neonates, an ideal method for measuring hemodynamics should be noninvasive, continuous, real-time, and practical. While standard measurements such as blood pressure, heart rate, and pulse oximetry provide valuable information, they are not comprehensive enough to fully assess hemodynamics.

Nowadays, there are several emerging hemodynamic monitors that could be applied in neonates. Bioimpedance-based cardiac output (CO) monitor, which offers the advantages of noninvasive and continuous measurement. This method provides a practical means to monitor trends in CO changes over time. Functional Doppler ultrasound can be employed to directly measure blood flow in major arteries, enabling assessment of end-organ perfusion. Near-infrared spectroscopy (NIRS) has been widely used to continuously monitor tissue oxygenation in target organs, particularly cerebral tissue saturation. NIRS offers the ability to track changes in oxygenation levels in real time, aiding in the early identification of cerebral hypoxia or hypoperfusion. Furthermore, amplitude-integrated electroencephalography (aEEG) can be utilized to measure brain activity, providing valuable insights into the cerebral tissue status of neonates.

The implementation of a neurocritical care bundle, which includes a range of multidisciplinary monitors, offers significant benefits in understanding and managing cerebral hemodynamics. This comprehensive approach empowers neonatologists to promptly identify cardiovascular compromise in the early stages and effectively respond to cerebral hypoxia or hypoperfusion. As a result, there is great potential for improved neurodevelopmental outcomes in neonates.

Gaining an early insight of precision medicine into the impact of perinatal hypoxia on the psycho-neurological disorders in childhood

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Background: Perinatal hypoxia is a noble cause of brain injury amongst the newborn, such injury often resulting in an increased risk of impaired performance as regards neuro-psychological disorders in later life for the affected individual. The development of molecular pathological mechanisms and feasible treatment strategies in precision medicine for neonatal hypoxic brain injury is an important verification topic for clinical translational medical human research in such patients. After such hypoxic brain injury, brain derived neurotrophic factor (BDNF: critical involvement in nerve cell regeneration and differentiation, synaptic neural network stability and maintenance, and central cognitive functions), the expression of BDNF protein was associated with learning and memory cognitive deficits in the later life.

Methods: In recent years, our laboratory has developed an innovation of non-invasive salivary biomarker detection technology for newborn based on the physique of neonates and the limited amount of analyzing samples. We have successfully verified the programing CpG sites for BDNF DNA promoter exon IV methylation, and simultaneous urine BDNF protein measurement in clinical hypoxic newborns.

Results: This study can also provide the development of related neurological biomarkers in early life and the establishment of a precision medical screening platform for therapeutic drugs. In addition, this study provides the viewpoint extension of various clinical insults in the developing brain (e.g., perinatal hypoxia with bacterial meningitis insults and neuronal damage due to maternal drug abuse) and serves as a molecular basis for BDNF-related epigenetic regulatory mechanisms.

Conclusion: We established a non-invasive detection tool to detect the degree of methylation of the neurological biomarker BDNF gene/CpG sequence position, and the degree of damage to the corresponding transcription factors with non-invasive salivary mucosa detection platform.

Congenital heart disease from children to adults

從兒童到成年人的先天性心臟病

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Because the recent advance of pediatric cardiology and cardiac surgery, the expected survival of patients with congenital heart disease (CHD) to the adulthood is improving in Taiwan. Most of the patients with CHD can survive and grow up into adulthood in the current era. At present, the adult patients (age above 18) accounted for 27.1% in all CHD patients in Taiwan. The prevalence of CHD was 2.17 per 1000 adult population. The new and complex medical issues about this specific patient group have posed a great challenge for the related health care providers. The most common problems encountered in this unique population including hemodynamic deterioration, heart failure, arrhythmias, other comorbidities and risks of stroke or sudden death. For women with congenital heart disease, evaluation and prevention of risk associated with pregnancy and delivery is also important. To ensure the care quality of adult patients with CHD, Adult Congenital Heart Center was established in National Taiwan University Hospital since November of 2008. Under the cooperation of experts in the pediatric cardiology, adult cardiology, cardiac surgery, radiology, anesthesiology, obstetrics and rehabilitation, the goals of this center are to educate these adult CHD patients about their malformed hearts, what to expect, and how to protect their interests most effectively. Most importantly, our center tries to provide an optimal transition from child-centered to adult-oriented care system and continuum of adult specific vocational assessment and professional medical management.

COVID-19: Current challenges and future perspectives

COVID-19 當前挑戰和未來前景

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Emerged in mainland China back in 2019, this highly transmissible virus, SARS-CoV-2, has gone beyond continents, infected at least 0.7 billion of people and claimed millions of lives. To cope with such a rampant virus, COVID-19 vaccines were developed in an unprecedented speed and seemed to have contributed to easing of the pandemic. The outstanding process of COVID-19 vaccine development has rewritten human vaccine history.

In response to this pandemic, Taiwan has been under level 3 warning since 15th May, 2020. Three years on, the notifiable disease was downgraded to flu-like illness on 1st May, 2023. Nevertheless, SARS-CoV-2 never leaves. It has adapted quickly to become more transmissible and changing to new variants from time to time. In face of this initially fatal and now highly changeable virus, what challenges are we facing and what are the future perspectives?

We will have an overview on the development of COVID-19 vaccines, effectiveness and safety of the currently available vaccines, current vaccine policy and antiviral treatment. Waning of the protective antibody raised the question of whether there is the need for booster dose. Evolution of new variants complicates the issue of developing new generation vaccines. More studies are needed to address the next unknowns, including optimizing future vaccine strategy in terms of design, number of doses, dosing interval, and approaches to achieve safe, durable, and even variant cross-protective immunity in both children and adults. As living with the virus is the trend now, development of anti-viral medication for all ages can be further explored.

Antibody-mediated rejection in pediatric kidney transplantation

兒童腎臟移植的抗體性排斥

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Kidney transplantation is the preferred treatment for pediatric patients with ESRD due to better patient survival, growth, and quality of life compared to chronic dialysis. Antibody-mediated rejection (AMR) after renal transplantation is defined by deterioration in graft function associated with the detection of donor-specific antibodies (DSA) to either human leukocyte antigen Class I and II (HLA) or non-human leukocyte antigen (nHLA) and characteristic histological features on biopsy. AMR remains to be a difficult-to-treat complication and leading cause of allograft failure in pediatric kidney transplant patients. Furthermore, allograft failure from AMR increases sensitization, rejection and graft failure in subsequent

re-transplantation in pediatric population because most of them likely require more than one graft in their lifetime.

Traditional treatments for AMR include plasmapheresis, intravenous immunoglobulin, and rituximab. Monotherapy or a combination of these treatments have varying efficacy for reducing DSA. The proteasome inhibitor Bortezomib induces the apoptosis of plasma cells may more effectively decrease DSA production and allow recovery from AMR. Bortezomib has been shown to effectively treat AMR. Some authors have advocated targeting interleukin-6 (IL-6) or IL-6 receptor (IL-6 R) as a promising therapeutic strategy. Imlifidase is a unique antibody-cleaving enzyme originating from Streptococcus pyogenes that specifically targets IgG and inhibits IgG-mediated immune responses. Imlifidase may represent a groundbreaking new method of desensitization.

AMR in pediatric kidney transplant continues to be a frustrating condition to treat because age-related differences in immunity and thus alloimmunity could contribute to variable responses to treatment. The clinician should prevent or at least detect AMR early before irreversible damage has occurred by routine DSA monitoring.

Autosomal recessive renal tubular dysgenesis: From bedside to bench

自體隱性腎小管發育不全：從病床到實驗室

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Autosomal recessive renal tubular dysgenesis (ARRTD) caused by inactivation mutations in *AGT*, *REN*, *ACE*, and *AGTR* is a very rare but fatal disorder with unknown prevalence. We firstly identified six Taiwanese with ARRTD from six unrelated families diagnosed by renal histology and molecular analysis. All patients exhibited antenatal oligohydramnios, postnatal anuria, pulmonary hypoplasia, and profound hypotension refractory to interventions. All but one died of profound hypotension, uremia, and pulmonary hypoplasia after birth. Identical homozygous E3_E4 del:2870bp deletion+9bp insertion in *AGT* (Angiotensinogen) were uncovered in all patients, and led to a truncated protein (1-292 amino acid). This mutation results in skipping of exons encoding the serpin domain of AGT, which is important for renin interaction and the generation of truncated protein. Serum AGT protein levels were diminished in the liver along with reduced serum AGT, angiotensin I (Ang I) and II (Ang II) levels. *In silico* modeling revealed a diminished interaction between mutant AGT and renin. Further in vitro study demonstrated that the expression of this truncated AGT protein was relatively low with a dose-dependent manner, and it diminished the interaction between mutant AGT and renin.

We firstly and successfully rescued one ARRTD patient with this *AGT* mutation by delivery of high-dose hydrocortisone therapy, with resolution of profound hypotension, accompanied by an increased serum AGT, Ang I, and Ang II levels. In vitro hepatocytes study, hydrocortisone increased the AGT level by accentuating the stability of mutant AGT and increasing its binding with renin. Hence, hydrocortisone may exert the therapeutic effect through the enhanced stability and interaction with renin of truncated AGT in patients carrying this *AGT* mutation. Due to all parents of affected patients harbored identical heterozygous mutation of *AGT*, we developed a novel TaqMan probe-based RT-PCR for conducting the prevalence of heterozygosity of AGT in Taiwan. The allelic frequency of this heterozygous *AGT* mutation was extra-ordinary high, suggesting that ARRTD may not be exceedingly rare in Taiwan.

New advances of gene therapy for Fabry mouse model

法布瑞氏症小鼠模型基因治療的新進展

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Fabry disease (FD) is an X-linked lysosomal storage disease caused by a deficiency in α-galactosidase A (GLA) activity, resulting from mutations in the GLA gene. The global incidence of FD is approximately 1 in 50,000, with a higher prevalence observed in Taiwan at approximately 1 in 1,600 individuals. GLA plays a crucial role in breaking down globotriaosylceramide (Gb3) within lysosomes. The absence of GLA activity leads to Gb3 accumulation in various tissues, causing cardiac, renal, and cerebrovascular damage and eventually death. Enzyme replacement therapy (ERT) is the current standard treatment for FD; however, it has limitations including a short protein half-life, frequent infusions, limited organ accessibility, and a non-curative nature.

Our team has explored the potential of adeno-associated virus (AAV) viral vectors encoding the GLA gene as a long-term treatment for FD in adult and neonatal mice. Our findings demonstrated that administration of AAV-GLA resulted in a substantial increase in GLA enzyme activity in the plasma, liver, heart, and kidney of FD mice. Remarkably, this heightened enzyme activity was sustained for at least 5 months. Furthermore, we observed a significant reduction in Gb3 accumulation in the kidneys of mice treated with AAV-GLA compared to untreated mice. Additionally, mice receiving AAV-GLA exhibited lower levels of anti-GLA antibodies compared to FD mice receiving ERT. These results highlight the potential of AAV-mediated gene therapy as a promising and effective therapeutic strategy for Fabry disease.

Taken together, our study provides encouraging evidence supporting the use of AAV-mediated gene therapy for FD treatment, with the potential to address the limitations associated with current ERT approaches. These findings contribute to the advancement of novel treatment options for Fabry disease and may have implications for future clinical trials in human patients.

Current studies of gene therapy for muscular dystrophies in Taiwan

台灣肌肉萎縮症基因治療研究之新進展

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Muscular dystrophies (MD) is a group of more than 120 genetic and debilitating muscle diseases that cause progressive weakness and degeneration of skeletal muscles. According to announcement of the Health Promotion Administration, Ministry of Health and Welfare in 19 April 2023, the MD on the list of rare diseases in Taiwan includes Duchenne muscular dystrophy (DMD)/ Becker Muscular Dystrophy (BMD), Myotonic dystrophy (MD), Facioscapulohumeral muscular dystrophy (FSHD), Limb-girdle muscular dystrophy (LGMD), Congenital muscular dystrophy CMD), and Emery–Dreifuss muscular dystrophy (EDMD). Unfortunately, treatments do not exist for the vast majority of MD patients.

Adeno-associated viral vector (AAV)-based gene therapy is an emerging and potential treatment for many types of MD. Treatments strategies based on AAV are being adapted for gene replacement corrects the disease by providing a functional copy of the gene and normal proteins, gene addition alleviates the disease by supplementing therapeutic genes that target a specific aspect of the disease mechanism, knockdown of dominant disease-causing genes using antisense oligonucleotides or inhibitory RNAs, delivery of gene editing tools such as therapeutic CRISPR/Cas9 genome editing and effecting alterations in pre-mRNA splicing and by manipulating expression levels of modifier genes. Translational and clinical trial work focused on these types of AAV treatments for DMD and various subtypes of LGMD including LGMD2B/ R2 (Dysferlin related), LGMD2C (Gamma-sarcoglycan deficiency), LGMD2D (Alpha-sarcoglycan deficiency) , LGMD2E/R4 (Beta-Sarcoglycan deficiency), and LGMD2I/R9 (FKRP related), with a focus on recent studies, pre-clinical large animal work and many promising ongoing and upcoming AAV clinical trials.

This presentation will report the current DMD patients received ASO treatment via managed access program, and the status of ongoing gene therapy trials in Taiwan.

Immunogenecity and toxicity of AAV gene therapy and possible treatment & prevention protocol

AAV 基因療法的免疫原性和毒性，以及可能的治療和預防計畫

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AAV (adeno-associated virus) gene therapy has demonstrated promising results in the treatment of genetic diseases. However, it is critical to address potential immunogenicity and toxicity concerns associated with this therapeutic approach. Immunogenicity refers to the response of the immune system to AAV vectors, including the production of neutralizing antibodies and cellular immune responses. Pre-existing immunity, resulting from prior exposure to AAV, can limit the effectiveness of therapy by neutralizing the vector and reducing its therapeutic benefit. Toxicity considerations, on the other hand, involve potential risks such as insertional mutagenesis, off-target effects, and inflammatory responses that can occur as a result of the gene therapy.

Treatment and prevention options involve immunosuppressive regimens, vector engineering, and combination therapies. Immunosuppression manages the immune response and enhances therapeutic efficacy. Vector engineering techniques aim to modify AAV vectors, such as capsid engineering, to reduce immunogenicity and enhance therapeutic potential. Combining gene therapy with other modalities, such as immunomodulatory drugs or anti-inflammatory drugs, may improve outcomes. It is important to note that specific protocols for AAV gene therapy, including management of immunogenicity and toxicity, may vary depending on the target disease, individual patient, and stage of clinical condition.

Addressing immunogenicity and toxicity challenges in AAV gene therapy is crucial for maximizing its effectiveness. Strategies such as immune modulation, vector engineering, and combination therapies are being explored to manage immune responses and reduce toxicity. Individualized protocols vary by disease, patient, and clinical stage, is critical to specific circumstances and to optimize patient outcomes.

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人工智慧在婦女醫療的應用暨國科會婦幼學門研究成果發表

Application of Artificial Intelligence in Women's Medicine and Achievement Presentation in the Discipline of Women's and Pediatric Medicine of National Science and Technology Council

時 間：112年7月8日 08:20~17:30

Time：July 8, 2023 08:20~17:30

地 點：臺北榮民總醫院 致德樓第二會議室

Place：The Second Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

人工智慧在婦女醫療的應用暨國科會婦幼學門研究成果發表

Application of Artificial Intelligence in Women's Medicine and Achievement Presentation in the Discipline of Women's and Pediatric Medicine of National Science and Technology Council

Pelvic muscle training combined with artificial intelligence

骨盆肌肉訓練結合人工智慧

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Urinary incontinence is a problem for many people, especially women. Pelvic muscle relaxation is one of the main causes of urinary incontinence. Therefore, we have researched and developed a non-invasive pelvic muscle training device that combines artificial intelligence technology to help patients perform pelvic muscle training at home to improve their urinary incontinence issues.

This training device allows patients, including elderly patients, to perform pelvic muscle training at home at any time, using voice guidance to train and record the patient's biofeedback data. Patients can also track their training progress through a smartphone application. By combining deep learning, we can analyze data such as training frequency, duration, and intensity to evaluate the effectiveness of the training. This data analysis can help doctors understand the patient's training progress to adjust training plans and provide better treatment recommendations to achieve optimal results.

We are applying artificial intelligence to the field of medical rehabilitation, aiming to quickly and effectively analyze the behaviors and characteristics of patients during their rehabilitation at home. Our goal is to not only help patients to perform more accurate self-rehabilitation training to improve treatment efficacy at home, but also assist doctors and physiatrists in obtaining sufficient rehabilitation information for urinary incontinence treatment, further improving patients' conditions and enhancing their quality of life, and providing them with a healthier future.

The future hospital: Perspective of developments in the digital transformation of the healthcare system

未來醫院：醫療數位轉型的發展與展望

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Globalization trends have focused on “value and effectiveness-oriented medical care.” Subsequently, digital medicine has emerged in recent years and become the focus of healthcare policy. Currently, our country already faces important challenges including the imbalance and uneven distribution of population structure, acceleration of interdisciplinary innovation, and catalytic transformation of digital technology. Therefore, in order to maintain the health of the working population and avoid disability, the development a precise healthcare model for chronic diseases is critical. Effective integration of medicine and technology, combined with the cooperation of clinical, engineering, legal, and industrial teams can help the hospital to catalyze the transformation of digital technology and establish a future hospital model. The key underlying the future hospital model is to effectively utilizing the massive medical data and the comprehensive establishment of the infra-structure of hospital information systems, which will then support the sustainable smart healthcare and the generation of the key knowledge economy of future healthcare.

Artificial Intelligence in the interpretation of Intrapartum electronic fetal monitoring

電子監測胎兒心音人工智能分析系統

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In the past, electronic fetal monitoring (EFM) systems provided a good moni.toring tool by various healthcare practitioners, including midwives, obstetricians, and labor and delivery nursing staff. The obstetric activities use EFM in fetal monitoring. The healthcare practitioners conduct real-time, longitudinal fetal monitoring services. Automatic and continuous monitoring of EFM in Artificial Intelligence mode promote the use of ubiquitous fetal monitoring services with real time status assessments requires a robust information platform equipped with an automatic diagnosis engine. Artificial Intelligence in the interpretation of Intrapartum electronic fetal monitoring describe an automated EFM data and capable of continuously and automatically analyzing EFM data. The abnormal events (heart rates and uterus contractions) are detected by the AI machine determination.

Laparoscopic dry box simulator training with assistance of artificial intelligence

腹腔鏡乾箱模擬教育以人工智慧訓練之路

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Laparoscopic dry box simulator training (DBST) is an efficient manner to enhance basic psychomotor skills and advanced suture techniques in minimally invasive surgery. Comparing with a complex simulator based on virtual reality technique, DBST does training on authentic material with tactile feedback. Meanwhile, DBS is portable and cost-effective, and could be adapted as a large-scale training tool. Currently, there is no artificial intelligence (AI) system to analyze, score and/or instruct DBST.

It's a step-by step route to facilitate an AI-assisted DBST: (1) to develop the exercises practical for enhancing basic psychomotor skills and advanced suture techniques; (2) to create validated scoring systems for assessing these exercises; (3) to originate an AI system to analyze the operating videos for scoring and instructing these exercises.

In our prior publication, a standardized origami practice called Origami Box Folding Exercise has been introduced with qualified expert validity to promote laparoscopic psychomotor skills. Meanwhile, a validated assessment tool in an objective structured assessment of technical skills format was published to score OBFE. In this speech, we would present Suture Cycle Exercise with its validated assessment tool in building up suture techniques, and in the meantime, the ongoing road to evolve an AI-assisted DBST.

Real-time intra-operative identification of malignant ovarian tumors using deep learning of clinical gross specimen images

術中卵巢腫瘤 AI 辨識系統

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Ovarian cancer is one of the most common gynecologic malignancies and has a high mortality. A proper operation strategy is key to improving patient prognosis. This study aims to develop a deep learning model that can be used an intraoperatively smartphone application to differentiate malignant from benign ovarian tumors based on gross specimen images. The retrospective study collected 662 cut-in-half gross images of specimens from 243 patients as a training dataset to develop convolutional neural network (CNN)-based models. Among the eight different CNN models, the MobileNet model had a better discriminating ability in classification (accuracy: 69.77%, recall: 61.84%, precision: 82.46%, AUC: 0.7149) and the performance was more precise than that of junior physicians (accuracy: 71.83%, recall: 80.48%, precision: 74.33%). The real-time intraoperative assessment of ovarian tumors using the mobile application has the potential to accelerate clinical decision making before obtaining pathology reports during the operation.

Menstrual improvements and GDF-15 in metformin-treated women with PCOS

多囊性卵巢女性在 Metformin 治療下的 GDF-15 變化與月經異常的影響

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Background: Metformin, a biguanide used in the treatment of type 2 diabetes, has recently been shown to increased production of GDF-15, which causes behavior changes resulting in significant weight decreases in mice. However, this relationship has not been evaluated in humans. Furthermore, since metformin is also used to treat PCOS, whether the change in GDF-15 is related to improvements in menstruation or hyperandrogenism is uncertain.

Methods: A cohort of 88 patients with PCOS were recruited, and were prescribed 500 to 2000 mg metformin per day. Patients were evaluated for changes in anthropometric measures, metabolic indices, hormonal indices, and menstrual regularity. Evaluations were performed before treatment, and after 3 months, 6 months, and 12 months. An age-matched control group was recruited for comparison.

Results: Patients with PCOS had significantly decreased levels of GDF-15, before and after adjusting for age and body weight. Significant increases in GDF-15 were seen in patients with PCOS who were treated with metformin, and there was significant dose-response curve. Changes in GDF-15 were significantly associated with improvements in anthropometrics, but not with improvements in menstrual regularity or androgen indices.

Conclusion: We demonstrate that changes in GDF-15, in response to treatment with metformin in patients with PCOS, is associated with improvements in metabolic indices, but not be the related to the improvements in hormonal and menstrual indices.

icONE--an AI-powered In vitro Companion Diagnostic Devices (IVD-CDx) for the future of precision personalized reproductive medicine

智能伴隨式輔助診斷系統在強化精準個人化生殖醫學的應用

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It was estimated that more than 15% of reproductive-aged couple are affected by infertility. According to the World Health Organization, infertility has become the third most serious health problem after cancer and heart disease. Even with helps from *in vitro* fertilization (IVF) technology, the successful rate barely reaches to 36%. With the additional support from the preimplantation genetic screening (PGS), the success event may go up to 50%. Nevertheless, the high cost and repeat cycles of IVF treatment have cause enormous burden psychologically and financially to the couples with such needs. As such, how to increase the implantation rate is the top concern and priority of the current precision and personalized maternal-fetal medicine in an IVF center! In order to reduce the number of cycles, diminish the risk associated with multiple pregnancy and maximize the efficacy of IVF treatment, we analyzed PGS data generated from 900 embryos to identify factors that are involved in embryo's viability and quality. Together with patient's clinical physiology and genetic information, we established a prediction model using three statistical algorithms including random forest to further explore the joint effects of these key factors on the successful implantation outcomes. A prototype of computer program, intelligent cOmputing Noble Embryo (icONE), was developed to precisely predict implantation outcomes following embryo transfer during IVF treatment using artificial intelligence. The specificity and sensitivity of icONE are 90.3% and 92.4%, respectively, and an overall accuracy of 91% was accomplished. An estimated reduction of 80% and 70% on the expended time and money was achieved. Although it is still in its infancy, icONE not only received the 18th National Innovation Award in year 2021 but also has been selected as the top 7 innovative technology among all the applicants, thus it suggests the advanced technique and profitable business value of icONE. We are currently working on the optimization and standardization of the system to complete product development and conduct clinical trials. The ultimate goal is to develop icONE into an "In vitro Companion Diagnostic Devices" (IVD-CDx) to provide AI-powered, cloud-based service. With the assistance from icONE to prioritize and rank embryos on their implantation potentials, reproductive medicine can finally realize its fantasy toward precision personalized medicine in the near future.

Application of Taiwanese health big data in reproductive study and beyonds

應用台灣人健康大數據於生殖醫學及其他研究

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Taiwanese Health care system is world well known, we provide the very available health care and establish the complete registry data set. These data set is the treasure for study in Taiwan. We can link national polulation registry data set, national birth data set, national ART data set, longitudinal health and welfare database, cancer and death registry to elaborate important health issue among reproduction and beyond. Here, we will describe the topic of "Neurodevelopmental disorders in offspring conceived via in vitro fertilization vs intracytoplasmic sperm injection" and "pelvic inflammatory disease is associated with ovarian cancer development in women with endometriosis: A cohort study in Taiwan" as models to study Taiwanese health big data.

Intracytoplasmic sperm injection (ICSI) is the most common method of assisted reproduction technology (ART). In Taiwan. ICSI becomes dominant, even reaches more than 90% utilization among ART in some ART center. The high utilization rate is for fear of fertilization failure and myth of high pregnancy rate in ICSI. We linked data from the national population registry data set, national birth data set and national ART data set for all live singleton births from January 1, 2008 to December 31, 2016. The results revealed ICSI does not increase the pregnancy rate , and surprisingly, we found ICSI had unfavorable implications for the neurodevelopmental health of offspring in terms of increased risks of autism spectrum disorder and developmental delay. Our study breaks the tale of ICSI and suggest we should select ICSI with cautious indication.

Besides the study of reproduction issue, we test the hypothesis of pelvic inflammatory disease are associated with ovarian cancer development in women with endometriosis. We selected patients who were diagnosed endometriosis or pelvic inflammatory disease between January 1, 2000 and December 31, 2015 in a 2 million longitudinal health and welfare database in Taiwan, then we link the data set with cancer and death registries. The results revealed the risk of ovarian cancer was significantly higher in women with endometriosis and subsequent pelvic inflammatory disease than in those with endometriosis alone. Our data showed pelvic inflammatory disease is associated with ovarian cancer in women with preexisting endometriosis.

The big data study can recruit large number of patients with long time series, and answer some clinical relevant important questions. However, we still need to improve and monitor the coding system to make the data valuable.

A novel pathogenesis of polycystic ovarian syndrome: The role of brain

多囊性卵巢症候群之大腦起源新解

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Polycystic ovary syndrome (PCOS) is one of the most common endocrine diseases in women of reproductive age. Women with PCOS are characterized with chronic anovulation, hyperandrogenism, and polycystic ovaries, as well as many metabolic abnormalities, such as obesity, hyperlipidemia, fatty liver, cardiovascular disease and diabetes, etc. Recently, it has also been found that women with PCOS have a higher prevalence of depression, anxiety, bipolar disorder, eating disorders and cognitive impairments and other mental and psychological related diseases than women without PCOS. The mechanism has not yet been fully clarified, and related pathogenic mechanisms have been proposed including: hyperandrogenism, insulin resistance and hyperinsulinemia, and abnormal brain structure or vascular perfusion, etc. Also, more attention has been paid to the research on the pathogenesis of neuroendocrine regulation in polycystic ovary syndrome. Previous studies have found that the hormones secreted at the hypothalamus and pituitary gland of women with PCOS are distinct from those of the control group. However, due to the difficulty in obtaining human brain tissue and the lack of good model organisms for this disease, it is very difficult to confirm the neuroendocrine-related pathogenesis of PCOS.

We have applied functional magnetic resonance imaging of the brain to study the relationship between brain imaging, psycho-mental representation and insulin resistance, ovulation and hormonal disturbance in women with PCOS. In addition, because induced pluripotent stem cells (iPSCs) are disease-specific and individual-specific, they can retain the original disease or individual cell characteristics, and might be used as a good cell model. Based on our previous successful experience to differentiate PCOS-specific iPSCs into ovarian granulosa cell and vascular endothelial cell, we have successfully differentiated the PCOS-specific iPSCs into hypothalamic cells. Such research will be used as a very important platform to explore the neuroendocrine-related mechanism of PCOS, hoping to clarify the pathogenic mechanism of PCOS from brain's perspective.

Molecular clue of endometriosis

探討子宮內膜異位症之分子機轉

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Endometriosis is a common but complicated gynecological disease, which affects about 10% of women in reproductive-age. Unfortunately, there is no cure for this disease and the etiology remains largely unknown. Recent advancements in biomedical research have enabled us to tackle many hard-to-treat diseases. With the state-of-the-art techniques and previously unrevealed scientific concepts, such as influence of functional noncoding RNAs or gastrointestinal microbiota on disease etiology and effects of epigenetic modifications or exosomes on disease progression, we might discover the hidden treasure for disease eradication. Our previous and current studies prove that hypoxia is an important factor that regulates numerous pathophysiological processes such as angiogenesis, glucose metabolism, cell cycle regulation, and drug resistance. Levels of hypoxia inducible factor-1α (HIF-1α) are elevated in ectopic endometriotic stromal cells. Upregulation of HIF-1α alters the expression of numerous critical genes controlling important pathophysiological processes during the development and progression of endometriosis. Compelling evidence demonstrates that histone modification, microRNA expression, and DNA methylation are involved in the regulation of genes contributing to the pathogenesis of endometriosis and are triggered by hypoxic stress. In this seminar, I will briefly summarize our recent findings in identifying mechanisms responsible for pathophysiology of endometriosis and demonstrate that targeting hypoxia-mediated gene regulatory network may open a new horizon for the treatment of endometriosis.

Study the genetic and environmental factors of endometriosis

探討子宮內膜異位症之基因因子及環境因子

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To study the genetic and environmental factors of endometriosis, the genotypes, genome-wide association study (GWAS), and phthalate exposure were conducted in the Taiwanese population. Endometriosis shares similarities with several autoimmune diseases. The human leukocyte antigen (HLA)-C genotype is associated with several human autoimmune diseases. HLA-C is a ligand of killer cell immunoglobulin receptors (KIRs) and an essential regulator of natural killer cell activity associated with endometriosis progression. We found that the occurrence of HLA-C*03:03*01 was increased and a reduced number of killer cell immunoglobulin receptors (KIRs) 2DS2-positive individuals in endometriosis than in control groups.

To determine whether genetic predisposition to endometriosis varies depending on ethnicity and in association with expression quantitative trait loci (eQTL). Novel genetic variants that predispose individuals to endometriosis were identified using GWAS and replication. The cis-eQTL rs13126673 of inturned planar cell polarity protein (INTU) showed a significant association with INTU expression on endometriotic tissues from women with endometriosis.

To study the association between urinary phthalate metabolite levels, endometriosis, and their effects on human granulosa cells, liquid chromatography–tandem mass spectrometry was used to measure five urinary phthalates. Urinary mono-n-butyl phthalate (MnBP) levels were higher in patients with endometriosis than in controls. MnBP treatment altered the gene expression of baculoviral inhibitor of apoptosis repeat-containing 5 (BIRC5), mitotic checkpoint serine/threonine kinase beta (BUB1B), cell division cycle 20 (CDC20), cyclin B1, interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), inhibin-B, steroidogenic acute regulatory protein (StAR) and cytochrome cholesterol side-chain cleavage enzyme (P450scc) and attenuated the ratio of the mitochondrial membrane potential in human granulosa cells. Moreover, MnBP decreased the expression of the anti-Mullerian hormone.

These findings revealed the important genetic factors and suggest that MnBP concentration is associated with endometriosis and may affect the health and steroidogenesis of human granulosa cells.

The role of sialylation in gynecologic cancers

唾液酸化在婦科生殖道癌症的角色

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Sialylation (the covalent addition of sialic acid to the terminal end of glycoproteins or glycans), tightly regulated cell- and microenvironment-specific process and orchestrated by sialyltransferases and sialidases (neuraminidases) family, is one of the posttranslational modifications, which plays an important biological role in the maintenance of normal physiology and involves many pathological dysfunctions.

Glycans have roles in all the cancer hallmarks, referring to capabilities acquired during all steps of cancer development to initiate malignant transformation (a driver of a malignant genotype), enable cancer cells to survive, proliferate, and metastasize (a consequence of a malignant phenotype), which includes sustaining proliferative signaling, evading growth suppressor, resisting cell apoptosis, enabling replicative immortality, inducing angiogenesis, reprogramming of energy metabolism, evading tumor destruction, accumulating inflammatory microenvironment, and activating invasion and accelerating metastases.

Regarding the important role of altered sialylation of cancers, further knowledge about the initiation and the consequences of altered sialylation pattern in tumor cells is needed, because all may offer a better chance for developing novel therapeutic strategy. In this review, we would like to update alteration of sialylation in female genital organs-related cancers.

3

膽胰惡性腫瘤內視鏡及藥物治療之新進展

Advances in Endoscopic Management and Pharmacologic Therapy for Pancreatic-Biliary Malignancy

協辦單位：台灣消化系醫學會、
台灣消化系內視鏡醫學會

時 間：112年7月8日 08:00~12:00
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Place：The Third Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

膽胰惡性腫瘤內視鏡及藥物治療之新進展

Advances in Endoscopic Management and Pharmacologic Therapy for Pancreatic-Biliary Malignancy

Advances in pharmacological therapy for pancreatic adenocarcinoma

胰臟腺癌藥物治療之新進展

Shao-Jung Hsu

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Pancreatic adenocarcinoma is the leading cause of death and increases over time. Pharmacological treatment of pancreatic adenocarcinoma evolved over the past decades and improved prognosis. Gemcitabine based regimen and FOLFIRNOX effectively prolonged survival in various stages of disease. In selective patients, targeted therapies provide new treatment options. However, surgical resection remains the potential cure treatment. As a result, a reasonable screening method in high-risk individuals is still an important issue. In this section, we will discuss the new progress in pharmacological therapy and challenges in early diagnosis.

Advances in pharmacological therapy for cholangiocarcinoma

膽管癌藥物治療之新進展

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Cholangiocarcinoma (CCA) is the second most commonly occurring primary hepatobiliary cancer, and is often diagnosed at an advanced stage. Despite the advances in understanding the biology of CCA during the last decade, and prognosis remain dismal. Chemotherapy with cisplatin and gemcitabine followed by second-line FOLFOX has been the cornerstone of treatment for patients with unresectable CCA in the last decade. Immunotherapy has also emerged as a potent strategy in combination with chemotherapy for CCA. The addition of durvalumab to cisplatin-gemcitabine chemotherapy showed a survival benefit in the TOPAZ-1 trial. Progress in the molecular understanding of CCA and the identification of druggable targets, such as FGFR2 fusions and IDH1 mutations, HER2 amplification, BRAF V600E mutation and others, has provided new treatment options. This strategy opened the way to personalized medicine for patients which are still fit after first-line treatment. In this topic, we provide an overview of evolution of systemic therapies to treat advanced CCA, and summarize recent clinical trial findings for patients with advanced CCA.

Advances in tissue acquisition methods for pancreatic-biliary neoplasms

膽胰腫瘤組織取樣術之新進展

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Pancreatic ductal adenocarcinoma is speculated to become the second leading cause of cancer-related mortality by 2030. Endoscopic ultrasound (EUS)-guided tissue acquisition (TA) is increasingly applied for the diagnosis of pancreatic solid masses. EUS-TA can be divided into EUS-fine needle aspiration (FNA) using Menghini needles, and EUS-fine needle biopsy (FNB) using Franseen or fork-tip needles. FNA and FNB are recommended equally for sampling of pancreatic masses, but some evidences suggest that the use of FNB results in more tissue and higher diagnostic accuracy with fewer needle passes then FNA, which may be relevant in cases where core tissue is required for diagnosis or genetic profiling, or when rapid onsite evaluation is not available. Endoscopic TA is also essential for diagnosing suspected malignant biliary stricture. Transpapillary standard biliary brush cytology and/or forceps biopsy can be considered for suspected malignant biliary strictures, but both with limited overall diagnostic sensitivity. Peroral cholangioscopy (PCA) and/or EUS-guided TA are suggested in indeterminate biliary strictures. POC may be preferable for proximal and intrinsic strictures, whereas EUS-guided TA may be preferable for distal and extrinsic strictures. The choice of TA modalities for biliary strictures depends on the clinical setting, the location of lesion and expertise. In this topic, we will discuss the advances in tissue acquisition methods for pancreatic-biliary neoplasms.

Endoscopic treatment for malignant gastric-duodenal obstruction

惡性胃十二指腸阻塞之內視鏡治療

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鄒永寬

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Malignant gastric outlet obstruction (MGOO) is a clinical syndrome characterized by upper abdominal pain and postprandial vomiting, mainly caused by tumor obstruction in the distal stomach, pylorus, or duodenum. The most common causes of MGOO are intrinsic gastric or duodenal neoplasms and extrinsic pancreatic or biliary malignancies. In the past, these patients would have been treated with surgical gastrojejunostomy (GJ). With the advancement of endoscopic treatment with minimally invasive properties, placement of luminal self-expanding metal stents (SEMS) may become an alternative to surgical GJ in most cases. However, in our experience, the patency duration of luminal SEMS for MGOO is approximately 4 months. Patients with an obstruction below the major papilla had slightly longer stent patency than those above the major papilla (median, 156 days vs. 123 days, $p = 0.511$). With improved treatment, the survival of MGOO patients has increased from 3-6 months to nearly a year. Therefore, the problem of enteric SEMS comes, mainly from stent obstruction requiring re-intervention. Less invasive therapies (compared to surgical GJ) with longer patency duration are needed. With the development of lumen-apposing metal stents, endoscopic ultrasound-guided GJ has emerged as a potential alternative to traditional surgical and endoscopic approaches. However, it should be emphasized that EUS-GJ remains a technically complex procedure. In this presentation, the treatment of MGOO will be discussed in detail.

EUS-guided biliary and pancreatic duct drainage

經內視鏡超音波導引之膽胰管引流術

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Endoscopic retrograde cholangiopancreatography (ERCP) is an established modality for the diagnosis and treatment of biliary and pancreatic diseases. However, there are cases in which ERCP is difficult due to duodenal obstruction, difficulty in bile duct and pancreatic duct cannulation, and anatomical reasons such as surgical altered anatomy. The advent of linear scopes has enabled the sampling of tissue specimens by EUS, and the therapeutic indications of EUS have also been expanded. Interventional EUS (IV-EUS) includes therapeutic procedures such as biliary drainage and antegrade stenting. Moreover, the rendezvous technique is used when cannulation is difficult. There are also reports of EUS-guided techniques to secure the approach route and remove stones. As for the pancreatic duct, IV-EUS has reportedly been carried out for pancreatic duct drainage and antegrade stenting. Furthermore, the rendezvous technique is also used. In terms of biliary drainage, this procedure is mainly performed for the palliation of obstructive jaundice in patients with malignant diseases who have failed biliary drainage by ERCP. The procedure is mainly divided into three methods according to the anatomical site of the fistula: EUS-guided choledochoduodenostomy (EUS-CDS), EUS-guided hepaticogastrostomy (EUS-HGS), and EUS-guided gallbladder drainage (EUS-GBD). As for techniques of EUS-guided biliary drainage, the echoendoscope is advanced into gastrointestinal tract, the biliary tract is punctured by a EUS-FNA needle. The guidewire is then advanced into the biliary system followed by dilation of the fistula. Finally, the stent is deployed between the biliary system and the gastrointestinal tract. EUS-guided pancreatic duct drainage (EUS-PD) is basically performed with the similar technique as biliary drainage, EUS-PD is considered as the most difficult procedure and requires various techniques to achieve successful treatment. EUS-BD and EUS-PD have attracted attention as a promising methods of alternative to ERCP, however, they lack dedicated devices and are technically still challenging.

ERCP-directed radiofrequency ablation

經膽胰管內視鏡之熱射頻消融術

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Radiofrequency ablation (RFA) is a well-established locoregional thermal ablative treatment method that causes coagulative necrosis and eventually leads to local destruction of many malignancies. RFA has been increasingly used for local control of premalignant and malignant tumors.

During RFA, an active electrode at the tip of a specifically designed catheter creates a high-frequency alternating current. The subsequent thermal damage leads to coagulative necrosis and cellular death once the target temperature exceeds 48-50°C. Intracellular components such as heat shock proteins release after tumor necrosis and can cause immunologic reactions which activate antigen-presenting cells and enhance immunity directed against the tumor.

Initially, RFA catheters were developed to perform through a surgical or a percutaneous route. Recently, a biliary RFA catheter working over the guidewire has been developed and showed its safety and effectiveness in the animal study. In subsequent studies, RFA has been used to increase stent patency in patients with malignant biliary strictures.

Biliary RFA has been shown that it appears to be a promising adjuvant local treatment method. It can be applied for malignant biliary stricture, bile duct involvement of ampulla adenoma or occluded SEMS by tumor ingrowth. The results of studies so far have suggested that biliary RFA can be technically feasible, can improve stent patency and patients' survival, and can be safely performed without serious AE. A prospective randomized trial compared biliary RFA with other treatment modalities such as PDT or radiation therapy is necessary. Biliary RFA can expand its indication to various biliary disease in the future.

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榮總三總中研院合作研究計畫成果發表會

Result Presentations of the Cooperative Research Project of Taipei Veterans General Hospital, Tri-Service General Hospital, and Academia Sinica

合辦單位：三軍總醫院、臺北榮民總醫院
協辦單位：中研院、臺中榮民總醫院、高雄榮民總醫院

時　間：112年7月8日　　08:30-12:00
Time：July 8, 2023　　08:30-12:00

地　點：臺北榮民總醫院 致德樓第四會議室
Place：The Fourth Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

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血管生物力學在透析血管併發症的臨床應用

Clinical Implications of Vascular Mechanobiology in Hemodialysis Vascular Access Complications

時 間：112年7月8日 08:20~12:00

Time：July 8, 2023 08:20~12:00

地 點：臺北榮民總醫院 致德樓第五會議室

Place：The Fifth Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

血管生物力學在透析血管併發症的臨床應用

Clinical Implications of Vascular Mechanobiology in Hemodialysis Vascular Access Complications

Biomechanics of hemodialysis vascular access

透析血管的生物力學

Yan-Ting Shiu

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The prevalence of end-stage kidney disease (ESKD) has continued to grow worldwide. Hemodialysis is the preferred renal replacement modality in many developed countries. The site on the patient's body where blood is removed and returned during dialysis is called a vascular access and is surgically created, because normal blood vessels do not safely provide the high blood flow rate required for this procedure. Although the vascular access is the lifeline for patients relying on hemodialysis to sustain their life, vascular access failure is a major cause of morbidity and hospitalization in this population. Maintaining functional access to support dialysis remains the most costly and challenging component of ESKD care.

There are two types of vascular access for chronic hemodialysis: an arteriovenous fistula (AVF), where an artery and a vein are connected directly, and an arteriovenous graft (AVG), where an artery and a vein are connected through a piece of plastic tubing. Since their inventions in the 1960's, AVFs and AVGs have continued to have high failure rates, with AVF non-maturation and AVG stenosis being the most common respective causes. Currently, no proven effective strategies exist for preventing their failure.

Central to devising strategies to prevent AVF and AVG failure is a complete mechanistic understanding of the pathophysiological processes. In AVFs and AVGs, shunting of arterial blood flow directly into the vein drastically alters the hemodynamic stress and wall stress in the vein. While it has long been appreciated that these biomechanical changes are likely major contributors to AVF non-maturation and AVG stenosis, detailed hemodynamic and wall stresses in the arteriovenous conduits have not yet been fully understood, partly due to a lack of tools.

This presentation provides an overview of the state-of-the-art methods for characterizing blood flow and wall deformation and calculating hemodynamic and wall stresses in arteriovenous access. This presentation will also discuss the recent advances in a typical patient-specific biomechanical simulation pipeline and the recent development of combining patient-specific models with machine-learning methods to obtain biomechanical factors faster and cheaper than conventional methods. These advances enable personalized biomechanical analysis, paving the way for developing personalized therapies for maintaining functional access.

Hemodialysis vascular access complications: Causes, detection, and prediction

透析血管併發症的成因、偵測、及預測

Chih-Yu Yang

楊智宇

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臺北榮民總醫院 內科部 腎臟科 及 國立陽明交通大學 醫學院 臨床醫學研究所

Chronic kidney disease is a prevalent health issue in Taiwan, with the current population receiving dialysis therapy reaching 90,000 and approximately 12,000 new dialysis patients each year. Hemodialysis vascular access, considered the lifeline of hemodialysis patients, is created by vascular surgeons through the anastomosis of the upper limb artery and superficial vein, forming the so-called “hemodialysis vascular access.” This vascular access provides sufficient blood flow for high-quality hemodialysis therapy, and vascular access dysfunction significantly impacts patients’ health.

Our research team utilized interdisciplinary research approaches, including microfluidic shearing experiments, animal models, vascular images of patients for fluid dynamics analysis, access flow surveillance and analysis, the development of an ambulatory optical sensor for access flow detection, and machine learning algorithms to study vascular access complications. These methods were employed to investigate the causes of vascular access complications and to detect and predict them effectively.

This presentation will cover our team’s experience in scientific research, combining precision medicine and translational research to decipher molecular mechanisms, improve clinical diagnostic accuracy, and promote the vascular health of hemodialysis patients. Regarding clinical services of our institute, we established an integrated interdisciplinary vascular care team to provide comprehensive vascular care and treatment for hemodialysis patients. Through a feedback loop involving physicians, nurses, case managers, and radiologists, we can detect vascular access dysfunction early and arrange proper treatments promptly. This approach offers specialized and attentive vascular care services for hemodialysis patients.

Vascular biology in the treatment of vascular access complications in hemodialysis patients

透析血管併發症相關治療的血管生物學

Timmy Lee

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The dialysis vascular access serves as the lifeline for the hemodialysis patient. It serves as the conduit for the hemodialysis patient to receive sustained dialysis therapy. The arteriovenous fistula (AVF) is the preferred vascular access for hemodialysis patients because it has lower frequency of thrombosis, infection, and healthcare-related expenses, if it successfully matures for dialysis.

A large proportion of AVFs created fail to successfully mature for dialysis (AVF maturation failure) and require assisted interventions for successful dialysis use. At present, there are few if any effective therapies to prevent AVF maturation failure because of the poor understanding of the pathophysiology of AVF maturation failure.

AVF maturation failure is most commonly characterized on angiography by stenosis at the juxta-anastomotic region of the AVF. The two main processes that lead to this juxta-anastomotic stenosis are impaired outward remodeling and flow- limiting intimal hyperplasia after AVF creation[1]. The mechanisms that govern inadequate outward remodeling and intimal hyperplasia remain poorly understood but are related to mechanisms that regulate endothelial function, inflammation, oxidative stress, and other vascular injury mechanisms. Aberrant hemodynamics after AVF creation also impact these vascular biological mechanisms and pathways. Thus, elucidating mechanisms of AVF maturation failure will assist in identifying new therapeutic targets and development of novel local therapies to improve AVF maturation failure.

Finally, there are also new and innovative technologies in biomedical engineering (i.e transcriptomics, proteomics, metabolomics) and biomaterials (i.e. novel drug delivery systems) that will help accelerate advancing our knowledge in understanding the biology of AVF maturation failure and development of novel therapies. The ultimate strategy to improve AVF maturation outcomes is to have “the right therapy, for the right patient, at the right time, for the right reason”.

Exploring molecular mechanisms of AVF remodeling: The journey to discovering medical treatments for improving AVF patency

探索動靜脈瘻管重塑之分子機轉：找尋改善瘻管暢通率藥物治療之路

Chung-Te Liu

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While the patency of arteriovenous fistula (AVF) is essential for hemodialysis treatment efficacy, effective medical treatment to improve AVF patency remains lacking. Currently, various cardiovascular medications have also been used to maintain AVF patency. Nonetheless, due to completely different pathogenesis between atherosclerosis and AVF stenosis, these attempts did not consistently show a beneficial effect on AVF patency. As such, to discover the medical treatment for improving AVF patency, we need to investigate the entire process of AVF remodeling, from how AVF maturation occurs to how AVF wall thickening causes stenosis.

Once AVF is created, its venous limb is exposed to arterial blood flow and subsequently dilates to accommodate increased blood flow. As an adaptation process, AVF wall thickens to sustain increased blood pressure. This remodeling process forms a functional AVF for hemodialysis, which is called AVF maturation. In some patients, vascular thickening continues to invade luminal space after AVF maturation, which ultimately leads to AVF stenosis.

To date, the predominant theory of AVF stenosis is that subintimal myofibroblast proliferation invades luminal space. However, in our preliminary data, we found that myofibroblast proliferation occurs in both AVF maturation and stenosis, which seems to be a continuous process. In the author's previous works, we had investigated signaling pathways that are activated during the process of AVF remodeling, including the activation of β-catenin signaling and increased expression of integrin subunit β6 in mouse aortocaval AVF model and pressure-culture system simulating the stretching pressure in the environment of AVF. In this report, we will review the results of these previous works. In addition, we will preliminarily reveal some unpublished data of how these signals express in human AVF specimens.

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在日常治療中再現臨床試驗功效

Projecting Clinical Trial Efficacy into Daily Practice

時　間：112年7月8日　08:30~12:00

Time：July 8, 2023　08:30~12:00

地　點：臺北榮民總醫院 致德樓第六、七會議室

Place：The Conference Room 6&7, Chih-Teh Building
Taipei Veterans General Hospital

在日常治療中再現臨床試驗功效
Projecting Clinical Trial Efficacy into Daily Practice

Optimized surgical planning after neoadjuvant therapy in breast cancer

打造術前藥物治療後最佳優化的乳癌手術計畫

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Neoadjuvant systemic therapy (NST) is conducted in a raised proportions of breast cancer patients, especially in HER2-positive or triple negative early breast cancer. It provides a strategy of downstaging to minimize the extent of surgery, also a platform to allocate patients in different risks. Advanced regimens including immunotherapy or novel targeted drugs lead to incremental improvements to attain pathological complete response, and even in event-free survival in several studies. Therefore, the crucial question after NST will be how to tailor the surgical plan in the propose of radicality. The role of multidisciplinary team is important to frame the surgical plan before and after NST. By contrast, another question is the possibility to eliminate breast cancer surgery. Several pilot studies had demonstrated that vacuum-assisted biopsy is feasible with promising results to determine pathological response and omit the surgery after NST in highly selected patients. Here we introduce the updated concepts of breast cancer surgery in the era of NST to balance high efficacy of novel agents and minimal invasive approaches.

Cardiac toxicity from breast cancer treatment: Can we avoid this?

乳癌藥物治療心毒性：治療藥物如何選擇及考量

Jiun-I Lai

賴峻毅

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Medical treatment is an important and fundamental cornerstone of breast cancer treatment. Neoadjuvant and adjuvant chemotherapy, targeted therapy, and/or palliative medical therapy, are all vital treatment modalities for breast cancer.

Several of the anti-cancer modalities have known cardiotoxicity effects. Anthracyclines are well known chemotherapeutic drugs for both early and metastatic breast cancer regimen. Although anthracycline treatment is effective, the resultant cardiotoxicity is troublesome and must be taken into consideration. Many methods and approaches have been sought to mitigate this consequence, including the introduction of liposome based doxorubicin, more concerted effects of cardiac monitoring, and/or others approaches. Due to the important efficacy of anthracyclines, they still remain an important and inreplaceable option for breast cancer treatment.

Herceptin is an groundbreaking treatment regimen that has drastically changed breast cancer landscape. Cardiotoxicity was also observed in early trials of Herceptin based regimens. However, the mechanism of cardiotoxicity is distinct to anthracycline based regimens, and most cardiotoxicity of Herceptin can be reversed uneventfully with adequate discontinuation of the drug. With newer anti-HER2 therapeutic regimens, it is important to update the role of cardiotoxicity and how we should be aware of this phenomenon.

In this talk, I will review the history perspective of cardiotoxic drugs, as well as clinical analysis and updated review of newer-anti-HER2 drugs. This talk will provide more insights into considerations of cardiotoxicity and how to manage this adverse effect in the scope of treatment in breast cancer.

Current approaches of HER2 positive early breast cancer treatment

標靶治療對早期 HER2 陽性乳癌的臨床運用與效益

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黃其晟

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Breast cancer is a major health concern worldwide, and HER2 positive breast cancer is a subtype that is characterized by overexpression of the HER2 protein, leading to more aggressive disease progression. Current treatment of HER2 positive early breast cancer involve a multimodal approach, including surgery, radiotherapy, chemotherapy, and targeted therapies such as HER2 inhibitors.

Recent advances in the treatment of HER2 positive early breast cancer have focused on optimizing the use of existing therapies and developing new strategies to target HER2 positive tumors. One such approach is the use of combination therapies, such as dual HER2 blockade with trastuzumab and pertuzumab, which has been shown to improve survival outcomes in early-stage HER2 positive breast cancer. Additionally, the development of novel HER2-targeted agents, such as T-DM1, which combines trastuzumab with a potent cytotoxic agent, has shown promising results in patients with HER2 positive early breast cancer who have residual disease after neoadjuvant therapy.

In conclusion, these target therapies offer hope for continued progress in improving outcomes for patients with HER2 positive early breast cancer.

Utilizing subcutaneous formulation of anti-HER2 therapies in breast cancer treatment

皮下注射劑型於 HER2 陽性乳癌治療之臨床應用

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Dual blockade target therapy of trastuzumab and pertuzumab combined with chemotherapy, has become the standard treatment of metastatic HER2+ breast cancer and node-positive early stage HER2+ breast cancer.

Subcutaneous administration of trastuzumab and pertuzumab offers patients a faster and more convenient treatment option. PHESGO is the subcutaneous injection form of both fixed dose trastuzumab and pertuzumab combining with hyaluronidase, an enzyme facilitating optimal local absorption.

Randomized studies have demonstrated that PHESGO is associated with similar efficacy and better tolerability. These data will be reviewed in detail in this presentation, along with several case studies.

The benefit of extended adjuvant therapy for HER2-positive early-stage patients in high-risk population

強化輔助治療在高復發風險 HER2 陽性乳癌患者的益處

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Breast cancer is by far the most frequent disease among women in Taiwan, and the diagnosis and treatment have also been improved a lot these years. HER2, the abbreviation of human epidermal growth factor receptor 2, could be one of the key biological factors in breast cancer category. The overexpression or amplification of HER2 gene could lead to cell abnormal progression, and it accounted for around 20% of breast cancer.

The application of trastuzumab significantly improved the clinical outcome of early stage HER2-positive breast cancer, nevertheless, nearly 30% of patients who had trastuzumab still faced recurrence risk within 10 years. Moreover, there are some other factors, such as nodal status, hormone receptor status, and achieving pCR or not, may influence the risk of recurrence.

Neratinib, an irreversible tyrosine kinase inhibitor, showed its efficacy with a different mechanism from mono-clonal antibodies, making it an option to extend patients' adjuvant treatment with a better outcome, especially for those who had a higher risk of recurrence than others. ExteNET trial demonstrated neratinib lowered 27% of recurrence risk in a 5-year follow-up period. The study also showed that the benefit of extended adjuvant therapy is higher in subgroups with a higher risk, such as non-pCR population.

This benefit has also been recognized by international guidelines, including NCCN, ESMO, and ASCO, suggests that 1-year extended adjuvant treatment should be considered for patients who have a higher risk.

Solving the risk of brain metastases in HER2-positive patients with tyrosine kinase inhibitor

用 TKI 解決 HER2 陽性乳癌患者的腦轉移風險

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With the application of anti-HER2 regimens, patients with metastatic HER2-positive breast cancer lived longer than before. However, the development of brain metastases still a problem for these patients, especially for those subtypes which had a higher chance to develop brain metastatic breast cancer, such as HER2-positive breast cancer. Up to 50% of patients with HER2-positive breast cancer develop brain metastases during their illness, suggesting it is still an unmet need for them.

In adjuvant setting, studies showed that neither dual-blockade nor T-DM1 lower CNS risk, and the addition of lapatinib to trastuzumab cannot bring positive result either. In ExteNET trial, neratinib arm showed a numerical improvement compared to placebo arm in CNS recurrence in a 5-year follow-up period. Moreover, neratinib demonstrated a significantly better 5-year CNS-DFS than placebo in HR-positive population who started the treatment within 1 year after trastuzumab. This result suggest neratinib could provide a potential CNS protection in adjuvant setting in early stage.

In metastatic stage, lapatinib is reimbursed among HER2-positive breast cancer patients with brain metastasis, and neratinib has been proved a better efficacy in NALA trial. Otherwise, TBCRC 022 also indicated that the CNS efficacy of neratinib among post-lapatinib patients and combination with T-DM1. In HER2CLIMB, tucatinib also showed its CNS benefit than placebo. With different mechanism from monoclonal antibodies and ADCs, TKIs have a chance to show their promising CNS benefit in HER-positive brain metastatic breast cancer, in both early-stage and metastatic setting.

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肺癌早期偵測計畫及早期肺癌治療

Early Detection and Treatment of Primary Lung Cancer

時 間：112年7月8日 08:30~12:00

Time：July 8, 2023 08:30~12:00

地 點：臺北榮民總醫院 致德樓第八、九會議室

Place：The Conference Room 8&9, Chih-Teh Building
Taipei Veterans General Hospital

肺癌早期偵測計畫及早期肺癌治療
Early Detection and Treatment of Primary Lung Cancer

Early detection and treatment of primary lung cancer

肺癌早期偵測計畫及早期肺癌治療

In 2011, the U.S.-based National Lung Screening Trial (NLST) showed the annual computed tomographic (CT) screenings resulted in 20% lower mortality from lung cancer than screening with the use of chest radiography. The result was also noted in 2020, the Dutch–Belgian lung-cancer screening trial, a population-based, randomized, controlled trial aimed to show a reduction in lung-cancer mortality of 25% with volume-based, low-dose CT lung-cancer screening in high-risk male participants at 10 years of follow-up.

Lung cancer in East Asia is characterized by a high percentage of never-smokers, early onset and predominant EGFR mutations, different from those in western countries, such as the United States. Only 5.9% of female patients with lung cancer in Taiwan have a history of smoking. Since 2014, the Ministry of Health and Welfare subsidized Taiwan Lung Cancer Screening for Never-Smoker Trial (TALENT) project to identify nonsmoking related risk factors for lung cancer. The first round of screening results revealed that relative to other groups at high risk for lung cancer, those with a family history of lung cancer have a high detection rate of lung cancer.

Since July, 2022, the Ministry of Health and Welfare launched the Lung Cancer Early Detection Program to provide biannual low-dose CT screening for high-risk groups: (1) individuals with a family history of lung cancer, specifically, men aged between 50 and 74 years and women aged between 45 and 74 years whose parents, children, or siblings have been diagnosed as having lung cancer, and (2) individuals with a history of heavy smoking, specifically, individuals aged between 50 and 74 years with a smoking history of 30 or more pack-years who are willing to quit smoking or who have quit smoking within the past 15 years .

Taiwan is the first country to provide lung screening for heavy smokers and individuals with a family history of lung cancer, thereby demonstrating the government’s thorough efforts to protect citizen health. The experience in radiologic features, cancer screening strategy in different department and preliminary result of low dose CT screening in different cancer center will be shared and discussed.

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智慧長照－多元連續的創新醫療照護

Smart Long-Term Care - Innovative and Continuous Multidimensional Medical Care

時 間：112年7月8日 08:30~12:00

Time：July 8, 2023 08:30~12:00

地 點：臺北榮民總醫院 致德樓第十會議室

Place：The Tenth Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

智慧長照－多元連續的創新醫療照護

Smart Long-Term Care - Innovative and Continuous Multidimensional Medical Care

Technology application of smart homes for the elderly

高齡智慧住宅之科技應用

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Taiwan will become a super-aged society by 2025. Elderly living alone and aging in place will become a new normal. The elderly have diverse needs, and technology-assisted aging in place is an important opportunity to provide safe, convenient, comfortable and happy living environment services for the elderly at home.

For elderly care in smart homes, the main focus includes the needs of the elderly and caregivers. Important needs include emergency accident prevention, health management, physical function enhancement, psychological state enhancement, and nursing activity assistance.

The technology applications of smart homes for the elderly can include physiological data management, motion data management, electrical appliance alerts and automatic shut-off, household assistance, audio-visual entertainment and therapy, indoor environmental quality management, and regulating technology. The most important aspect of these smart technology applications is the establishment of a networked environment.

The future trend is to develop an inventory of aging-friendly home environments, which includes universal technology products, and to establish scenarios for these implementations. When planning home environments, it is necessary to consider the integration of technology products and application scenarios in advance. Space planning includes power supply, sockets, network environments, and consideration of the coordination of activity spaces for robots, to meet the needs of elderly people with health issues, sub-health conditions, special needs, and physical and mental disabilities.

Lessons learned - Implementing smart technologies in long-term care facilities

智慧科技運用於長照機構之前瞻發展建議

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元智大學 老人福祉科技研究中心

Facing widespread population aging, people naturally consider applying technologies to provide positive solutions in maximizing the efficiency and effectiveness of the workforce and resources for the care of older adults. Gerontechnology is an emerging interdisciplinary field that has received attention worldwide. After decades of development, many research projects and products aim to help older adults and their caregivers with technologies. However, few technological products have been widely adopted for the care of older adults. There is a huge barrier to overcome.

In January 2022, more than 3,000 smart mattresses were deployed in 12 veteran hospitals and nursing homes, which is by far the largest implementation project in Taiwan. We worked closely with caregivers to help them use the smart mattress and care system successfully. In addition to the many technical and management issues, the most important lesson we learned is to restructure the care system into a configurable one for evolving user needs. The care system should be scalable to various IT platforms, including the public cloud for general services (e.g., home users), hospital servers, and even a dedicated self-hosted mini server inside the nursing home for privacy concerns. For care system user interface (UI), we abandoned the one-size-fits-all approach to avoid overloading caregivers with data and alerts they do not need. We allowed caregivers to customize alert settings for patients/residents of different risks (e.g., falls, pressure injury, cognitive impairment) and configure the data display for the items they need the most. For example, hospital nurses hope to see the real-time status of all patients at a glance, while nursing home caregivers pay more attention to long-term data for adjusting the care program for each resident.

Gerontechnology is about designing for people, and caregivers are the best designers. Technology is not that important; it is how you use the technology. In the European AAL project, we aimed to allow caregivers to freely choose the combination of care products according to their care needs. The major research issue is integrating heterogeneous data into a dashboard as an entry point to descriptive/diagnosis analyses.

In these two government projects, we aim to provide caregivers with the motivation and successful experience in applying smart technologies in long-term care facilities. Lessons learned from these projects will be shared in this presentation.

Introducing smart assistive technology in the field of long-term care - The digital transformation experience of Gan-Dau Hospital

導入智慧輔助科技於長照場域：關渡醫院的數位轉型經驗

Nien-Tzu Kao
高念慈
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臺北市立關渡醫院

The introduction of smart assistive technology in the field of long-term care can greatly improve the quality of care, reduce the burden on caregivers, and provide more diverse and comprehensive care solutions. The following is the digital transformation experience of Gan-Dau Hospital:

1. Selection of the right technology: Choose the technology that can meet the actual needs, such as emergency call system, smart mattress, smart sensor, care robot, etc.
2. Establish a comprehensive database: The database should contain the basic information of users, care needs, medical records, drug use and other relevant information to help caregivers provide care more efficiently.
3. Intelligent auxiliary equipment: Equipment such as intelligent wheelchairs, intelligent crutches, intelligent medical beds, etc., to provide the elderly with more autonomy and safety in life. For example, a smart wheelchair can allow the elderly to walk independently, and can also automatically monitor and remind them to prevent the elderly from getting lost or falling.
4. Information-based care management: Through the information-based care management system, it is possible to effectively integrate the care information of the elderly, including health status, medication records, medical records, etc., and then provide comprehensive care solutions. At the same time, it can also interact with caregivers through the network platform, so that caregivers can understand the care needs of the elderly in real time.

Based on the above, the introduction of intelligent auxiliary technology can improve the quality and efficiency of long-term care institutions' care, and at the same time reduce the burden on caregivers, but it is necessary to pay attention to related risks and problems, and carry out effective management and control.

Application of smart devices in hospice palliative care: An example in Taipei Veterans Home

智慧裝置於安寧緩和照護的應用：以臺北榮民之家為例

Chaw-Mew Hung

洪嘉妙

Team of Healthe Care, Taipei Veterans Home of Veterans Affairs Council, New Taipei City, Taiwan, ROC

國軍退除役官兵輔導委員會臺北榮譽國民之家 保健組

Taipei Veterans Home is located in Baijishan, New Taipei City. It is a multi-level care institution that takes care of people with assisted living or nursing needs, or with dementia. It has a total of 718 beds and nearly 245 employees. The mean age of overall residents in Taipei Veterans Home is 84 years old, which is even higher among the residents in the nursing care area. Due to advanced age and comorbidities, the mortality rate of residents is high. Almost 100 residents died each year in the past three years in this Veterans Home. Therefore, we began to actively promote the palliative care model of long-term care institutions. The palliative care model of our institution is to cooperate with the home care team of Taipei Veterans General Hospital to form a cross-level cooperation, which can also be regarded as another result of the pyramid plan of the counseling association.

The dilemma of palliative care in Veterans Home is that we do not get more resources, such as manpower and material resources. But need pay more attention on residents when they accept palliative care. Therefore, we expect to use smart devices to improve care efficiency and reduce terminal discomfort symptoms at the end-of-life. We also look forward to reducing caregiver load.

Since 2021, our institution has introduced four smart devices—BestShape VS to the bedside of the residents who received palliative care. Through non-contact and continuous physiological measurement, results were found after use of these smart devices. First, Give voice to the disabled and provide announce when they were discomfort. 2 As a basis for morphine drug adjustment, relieve the pain and suffering of sore of breathe. 3 End-of-life notification, reduce the stress on caregivers and family members.

Sharing the experience of smart technology assisted medical and hospice care for long-term care facility residents

長照機構住民之智慧科技輔助醫療與安寧療護經驗分享

Yu-An Chang
張妤安
Taipei Noble Health Care & Rehabilitation, Taipei, Taiwan, ROC
臺北市私立貴族老人長期照顧中心

In the field of home-based medical care, it is often said that 'home is the best hospital'. For the elderly who reside in long-term care facilities due to chronic diseases, comorbidities, or disabilities, these facilities become their 'home'. As a result, ensuring a peaceful and dignified end-of-life experience for residents in these care facilities is of paramount importance.

With the assistance and guidance from the hospice care team of the Taipei Veterans General Hospital, our care staff have been able to enhance their professional skills through collaborative learning. This partnership has allowed us to extend the concept of integrated hospice care from hospital wards to long-term care facilities, providing comprehensive and comforting care for our residents. Furthermore, we have adopted smart care monitoring devices that continuously track residents' vital signs, alerting medical staff in a timely manner through Line group notifications when necessary, to ensure that residents receive proper care.

In summary, we share our experiences on implementing hospice care in long-term care facilities, as well as our collaborative experience with transdisciplinary professionals and the Taipei Veterans General Hospital's hospice care team. We hope that these experiences can serve as a reference for other long-term care facilities, working together to provide higher quality living care services for their residents.

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精準醫療系統再進化：
CiC整合服務溫度及創新數位科技

Re-evolution of Precision Medical System: CiC Integrates Warm Services and Innovative Digital Technology

時 間：112年7月8日 08:30~17:00

Time：July 8, 2023 08:30~17:00

地 點：臺北榮民總醫院 醫學科技大樓一樓會議室

Place：Medical Science and Technology Building
Taipei Veterans General Hospital

精準醫療系統再進化：CiC整合服務溫度及創新數位科技
Re-evolution of Precision Medical System: CiC Integrates Warm Services and Innovative Digital Technology

Why is it important for hospitals to prioritize data governance?

為什麼醫院要重視數據治理？

Herng Su

蘇蘅

University System of Taiwan, Hsinchu, Taiwan, ROC; and College of Communication, National Chengchi University, Taipei, Taiwan, ROC

臺灣聯合大學系統 及 國立政治大學 傳播學院

Global healthcare industry is quietly undergoing a revolution. In the coming years, we will witness the realization of Public Healthcare 4.0. Medical care, pharmaceuticals, and health safety are the most valuable aspects of human life. The development of information and communication technology (ICT) in public healthcare continues to create expanding market, but society also faces the dark forces that breach hospitals and health systems through ICT, collecting and/or tampering with the records of patients' monitoring, diagnosis, and treatment. Hospitals are among the top targets of hackers because of all the personal information they have stored about patients.

In the digital age, the medical data aggregation is crucial for the overall healthcare, emergency response, disaster relief, and health security of society. New healthcare privacy challenges as online data tracking, sharing methods evolve. Doctors, patients, hospitals, and governments need to actively confront the greater risks of data breaches, escalating costs, and the potential erosion of societal trust in hospitals.

The threats of cybersecurity and data governance to the entire healthcare sector, particularly hospitals, are increasingly important. Over the past decade, the medical field has experienced a massive digitalization. The health systems have lagged behind other industries in safeguarding its primary beneficiary - the patients. Presently, hospitals must allocate substantial financial resources and devote extensive efforts to protect their medical and healthcare facilities and devices. In addition, potential adversaries also need to be identified along with their intentions and capabilities. However, implementing these measures is considerably challenging in practice due to the inherent complexity of hospitals as organizations, characterized by high-quality technologies, medicine inventory, and intricate internal dynamics. As adversaries become more skilled, cyber threats in hospitals will probably continue to multiply and become more complex.

This lecture will provide new insights from recent academic researches of Harvard University, Massachusetts Institute of Technology (MIT), and other relevant institutions. Domestic and international significant cases are included.

Contact-free AI-based atrial fibrillation risk detection

零接觸式人工智慧心房顫動偵測

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吳炳飛

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國立陽明交通大學 電機工程學系

Atrial fibrillation is the most frequent cardiac arrhythmia. 17% of patients have no obvious symptoms, and three-quarters of patients do not know that they are sick at all before diagnosis. Therefore, atrial fibrillation is very difficult to detect. Atrial fibrillation is often discovered after a stroke happened. The technology of "Contact-Free AI-Based Atrial Fibrillation Risk Detection " can provide the ordinary people, sub-healthy groups, and patients with atrial fibrillation for their daily health records, or follow-up disease records after surgery.

The principle of the contact-free image-based atrial fibrillation(AF) discriminating system is based on the consistency that irregular cardiac cycles can both be detected on the waveforms of electrocardiography and remote photoplethysmography (rPPG). At the beginning of the detection, the quantity of the blood varies from time to time is captured through facial images taken by a general camera. The signals from RGB channels are then synthesized and processed through the core algorithm to eliminate noise disturbance and generate a stable rPPG signal simultaneously. In addition to the core algorithm, the face tracking algorithm has also been integrated into the front level of the system. It is used to ensure the region of interest on the human face could still be tracked down when the user is apparently moving. The processed signals are then classified as AF or not by neural networks. According to the IRB evaluation in En Chu Kong Hospital, the system can well detect AF with high accuracy.

The major breakthrough technology of video-based AF detection is only with a general camera and without an EKG or wearable device. This technology can be integrated into personal devices, such as smartphones, tablets, or PC. People can use the camera on personal devices to capture the image of the skin and then detect whether the atrial fibrillation happened or not.

Shaping the future of healthcare: Sharing global perspectives on intelligent healthcare ecosystem deployment strategies

全球智慧醫療生態系佈局策略分享

Ming Chih Chiang
江明志
Service-IoT Group,Advantech Co. Ltd.
研華科技智能服務事業群

Advantech is a global leader in the healthcare industry, driving innovation in AIoT digital transformation and intelligent healthcare services. We offer a comprehensive range of standardized products in medical computers, medical imaging, and medical mobility. Leveraging IT expertise through collaborations with healthcare brand accounts, Advantech ensures they remain at the forefront of intelligent healthcare solutions.

Advantech focuses on enhancing healthcare facilities with smart hospital solutions that integrate hardware and software from edge to cloud. This includes telehealth, intelligent outpatient services, intelligent wards, and surgical real-time video streaming and management. Advantech also enables hospital information integration, including 3D modeling utilization for data visualization, leveraging AI-assisted diagnosis, and intelligent building and energy management. Advantech iHealthcare solutions cater to specialized disciplines such as obstetrics, emergency rooms, ICU wards, and more.

To establish a global intelligent healthcare ecosystem, Advantech collaborates with system integrators, software vendors, healthcare institutions, IT platforms, and medical equipment vendors. We strategically implement business strategies tailored to different regions, adhering to international medical standards and obtaining relevant certifications. Advantech success is exemplified by implementing innovative hospital solutions in Vietnam's Thai Hoa General Hospital.

Despite regulations and data integration challenges, we believe collaboration among industry, government, and academia is crucial for the successful implementation and market adoption of intelligent healthcare products and solutions.

In summary, our dedication to the healthcare industry and expertise in AIoT and intelligent healthcare services positions Advantech as a global leader. Our intelligent hospital solutions, co-creation and collaborative approach, and adherence to international standards contribute to advancing intelligent healthcare worldwide.

Artificial intelligence applied to the diagnosis and prognosis of sudden sensorineural hearing loss

人工智能應用於突發性耳聾的診斷與預後

Wen-Huei Liao

廖文輝

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臺北榮民總醫院 耳鼻喉頭頸醫學部 耳科

Sudden sensorineural hearing loss (SSNHL) is an emergency disease, and its pathogenesis is still largely unknown, making it difficult to diagnose and develop a therapeutic strategy. We proposed a smartphone-based Ear Scale app to determine the diagnostic validity of hearing scale differences between the two ears for SSNHL.

To predict treatment outcomes and customize treatment strategies, we used a physician decision support system that incorporates complex information from electronic health records. We also developed a predictive model for complete recovery, defined as complete hearing recovery after treatment (final hearing ≤25 dB HL), using four machine learning models: LGBM classifier, XGBoost classifier, SnapDecisionTree classifier, and SnapLogisticRegression. Using the physician decision support system, we successfully identified two predictors associated with the highest odds of achieving complete hearing recovery (<25 dB) in patients with SSNHL: pretreatment hearing Grade 2 (26-45 dB) and treatment within ≤7 days of disease onset. According to the SHAP summary plot and PDP plot, factors such as age, pretreatment 4000 Hz frequency, BMI, cholesterol, and discriminant points were crucial in predicting complete hearing recovery.

The developed model provides an accurate and straightforward approach to identifying complete hearing recovery in individuals with sensorineural hearing loss. This can help prioritize hearing assessments and enhance decision-making for these patients. The proposed machine learning model has the potential to assist clinicians in timely and accurate prediction of hearing recovery rates, ultimately improving patient outcomes.

Intelligent innovation: Augmented reality-assisted cardiopulmonary rehabilitation program

擴增實境智慧創新應用於心肺復健經驗分享

Wan-Ting Chu

朱琬婷

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Cardiopulmonary rehabilitation provides integrated interventions including aerobic training, strengthening exercises, flexibility training, early mobility training, functional training and so on. The disease types of patients receiving cardiopulmonary rehabilitation include AMI, open heart surgery, heart failure, respiratory failure, post COVID-19, deconditioning, lung cancer...etc. Cardiopulmonary physical therapist prescribes individualized exercise prescription after complete evaluations. Patients could execute the exercise instructions by using educational leaflets in many places, such as hospitals, homes, working places.

Traditionally, educational leaflets with exercise instruction are handed to patients after physical therapy so that patients can practice accordingly. However, patients usually have low motivation to practice because educational leaflets are not as lively as videos. The department of physical rehabilitation collaborated with the Clinical Innovation Center (CIC) in 2010 to develop an Augmented Reality medical app (AR_App) for physical therapy,

The AR_App includes 6 upper limb exercises such as shoulder flexion and elbow flexion, 28 lower limb exercises such as ankle pumping and knee extension, and 8 cardiorespiratory exercises such as diaphragmatic deep breathing and chest expansion. Each exercise is accompanied by instructional videos recorded in Chinese, English, and Taiwanese by physical therapists and augmented by virtual coaching demonstrations. Patients can use their mobile phones or iPAD to correct their own movements through the device's camera and receive audio feedback and visual guidance to ensure correct movements. Physical therapists evaluate patients' joint mobility, muscle strength, and functional level and develop individualized exercise prescriptions. PT set up a user ID, exercise content, frequency, and total rounds per day for each patient. Patients can access the AR_App and use their ID by themselves.

With the development of technology, augmented reality can integrate users into the digital visual and audio interface, which may increase the motivation of patients to exercise.

Scientific debrief of CiC projects and poster- oral presentation

CIC 專案計畫成果彙報

Chia-Chang Huang

黃加璋

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臺北榮民總醫院 教學部 臨床技術訓練科

Clinical Innovation Center (CIC) of Taipei Veterans General Hospital was established since 2019. Total 32 projects were executed in 4 years and some projects are still on going. Total executive budget was NTD$ 7,446,967. The type of the innovation projects revealed service redesign with ten projects, technology innovation with eleven projects, product innovation with five projects, new media application with one projects and other types with five projects. Two projects were failed at first trail stage. Eight projects were failed at review stage. Two projects were passed but pending Institutional Review Board, IRB. The passing rate of innovation projects was 77.3 % in these 4 years.

Total six projects were accepted awards. Total three projects had got the patent. One project had got the trademark registration. Two projects are planning application the patent. Two projects had accepted oral presentations in conferences. Three projects had accepted Posters in conferences. Four projects had accepted five original papers in journals. Nine projects would have extension plan in the future. There were also many peripheral benefits and beneficiary groups from our innovation projects.

Thanks to the 32 project hosts who participated in our CIC innovation projects. Their hard work in innovation research and develop have revealed such rich results as mentioned. Total six to seven projects can be sponsored by the remaining budget of CIC. Welcome to continue investing in CIC.

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Precision medicine in emergency medicine: Saving lives in the blink of an eye

急診醫學之精準醫學意涵：拯救生命只在眨眼一瞬

Chung-Ting Chen

陳春廷

Emergency Department, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

臺北榮民總醫院 急診部

Precision medicine is an emerging approach that aims to provide customized medical care based on individual variability in genes, environment, and lifestyle. In emergency medicine, this approach can be particularly helpful in identifying the most effective treatments for patients with acute conditions. Genomics, a key component of precision medicine, plays a vital role in emergency medicine by helping identify patients who may be susceptible to severe reactions when exposed to certain medications, such as opioids. By conducting genomic analyses, healthcare professionals can uncover specific genetic markers or variations that may increase the risk of adverse drug reactions.

Apart from genetics, precision medicine in emergency medicine acknowledges the significance of environmental factors in understanding the underlying causes of a patient's symptoms. For example, if a patient presents with respiratory distress, doctors may take into account environmental considerations such as air quality and pollution levels in the surrounding area. By considering these factors, healthcare providers can gain a more comprehensive understanding of the patient's condition and determine the appropriate treatment plan. To effectively implement precision medicine in emergency medicine, the collection and analysis of vast amounts of data are crucial. This involves not only gathering and evaluating medical records but also incorporating information about a patient's genetic profile, environmental exposures, and lifestyle choices. By integrating these diverse datasets, healthcare providers can gain valuable insights and develop a comprehensive understanding of each patient's unique characteristics.

Ultimately, the goal of precision medicine in emergency medicine is to provide personalized and effective care that takes into account each patient's unique needs and circumstances. By considering the individual's genetic makeup, environmental factors, and lifestyle choices, healthcare providers can move away from a generalized approach and instead develop targeted interventions that optimize patient outcomes. With continued research and development, precision medicine has the potential to transform the field of emergency medicine by improving patient care, reducing adverse events, and fostering a deeper understanding of the intricate relationship between genes, environment, and health.

In conclusion, precision medicine represents a groundbreaking approach in emergency medicine, offering customized care based on individual genetic variability, environmental influences, and lifestyle factors. By leveraging genomics and considering environmental factors, healthcare providers can gain valuable insights into disease mechanisms and identify optimal treatment strategies. The successful implementation of precision medicine in emergency medicine relies on the integration and analysis of extensive datasets from various sources. The ultimate aim is to provide personalized and effective care that considers the unique needs and circumstances of each patient. With ongoing research and technological advancements, precision medicine holds the potential to revolutionize emergency medicine, leading to improved patient outcomes and a deeper understanding of the factors shaping individual health and well-being.

In-depth analysis of genomic information with polygenic risk score

利用多基因風險分數進行基因體資訊深度解析

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張家銘
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The health condition of individuals is closely related to their innate genes, combined with environmental factors, resulting in different traits and complex diseases. Therefore, genomic information is crucial for maintaining health. However, most health conditions are the result of the combined effects of multiple genes, through polygenic analysis, we can discover the hidden polygenic interactions within the genome, which leads to more accurate disease prediction. Currently, polygenic analysis primarily involves polygenic risk score (PRS). This technique requires the genomic information of the subjects and corresponding datasets from genomic association studies (GWAS) to calculate the risk for specific diseases. Therefore, in this presentation, I will focus on introducing PRS and its clinical implications. Furthermore, with the advancements in artificial intelligence technology, we anticipate the development of advanced analysis techniques that combine PRS with artificial intelligence.

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北科生醫健康園區智醫論壇

Intelligent Medicine Conference of Beitou Shilin Biotechnology Park

合辦單位：國立陽明交通大學
協辦單位：臺中榮民總醫院、高雄榮民總醫院
贊助單位：華碩文教基金會、廣達電腦公司、飛利浦台灣分公司

國科會前瞻司「回應國家重要挑戰人工智慧專案計畫」
國科會生科司「應用生醫資料庫開發新穎生物標記及疾病風險評估模式」計畫
臺北榮總放射線部

時　間：112年7月8日　　08:00~17:30
Time：July 8, 2023　　08:00~17:30

地　點：臺北榮民總醫院 介壽堂
Place：Jie Shou Hemorial Hall
Taipei Veterans General Hospital

北科生醫健康園區智醫論壇

Intelligent Medicine Conference of Beitou Shilin Biotechnology Park

10-1 Building digital health platform well to develop smart hospital excellent..... I-Ming Parng

10-2 Data journey optimization for AI medicine and precision health.....Ted Chang

10-3 Medical AI: From innovative ideas to landing applications.....Vincent S. Tseng

10-4 The implementation of artificial intelligence products: Experience in National Taiwan University Hospital.....Lu-Cheng Kuo

10-5 A proposed multi-criteria optimization approach to enhance clinical outcomes evaluation for diabetes care: A commentary .....Hsing Luh

10-6 Well-tempered patient journey by reconstructing information strategies - to demonstrate how the real world data of surgical cases were collected and communicated in Taipei Veterans General Hospital ..... Meng-Hsuan Chung

10-7 How instant and rapid whole-genome sequencing analysis helping clinicians and the limitations we are facing now.....Chia-Feng Yang

10-8 The application and perspective of artificial intelligence in retina.....De-Kuang Hwang

10-9 Generative AI and healthcare metaverse .....Lewis Chang

10-10 The transferable artificial intelligent model based on electrocardiogram: A prospective observational study toward home-based application of single-lead ECG in identifying heart failure with low left ventricular ejection fraction .....Men-Tzung Lo

10-11 Maximizing health through genomic information.....Chia-Ming Chang

10-12 Comprehensive AI-integrated ecg system-the experience from Tri-Service General Hospital..... Chin-Sheng Lin

10-13 Test-fairness deep learning with influence score.....Henry Horng-Shing Lu

Building digital health platform well to develop smart hospital excellent

建立完善數位醫療平台以發展卓越智慧醫院

I-Ming Parng

龐一鳴

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衛生福利部 資訊處

Building a digital health platform is crucial for developing a smart hospital that delivers high-quality, patient-centered care. The next-generation digital healthcare platform is designed to promote interoperability and compliance with international data exchange standards. In addition, the platform can create a scalable, flexible, robust infrastructure for smart hospitals by adopting containerization and microservice architecture.

Moreover, the digital platform can create significant healthcare marketing opportunities, boosting revenue and improving patient outcomes. The platform can help hospitals improve their services by leveraging emerging technologies such as artificial intelligence and smart healthcare. AI can help improve decision-making and diagnostic accuracy, while smart healthcare can help hospitals to collect and analyze data to improve operational efficiency.

Interoperability is a critical aspect of the digital platform as it enables seamless data exchange among different healthcare systems. Compliance with international data exchange standards such as FHIR is essential to ensure that healthcare data is exchanged standardized and securely.

In conclusion, building a digital health platform is key for developing a smart hospital that can provide high-quality, patient-centered care. It promotes interoperability, and compliance with international data exchange standards, creates healthcare marketing opportunities, and leverages emerging technologies such as artificial intelligence and smart healthcare to improve patient outcomes.

Data journey optimization for AI medicine and precision health

智慧醫療與精準健康的資料旅程優化

Ted Chang
張嘉淵
Quanta Computer Inc.
廣達電腦股份有限公司

Data driven AI is transforming healthcare and medicine for the future. Optimization of Data Journey to reshape Patient Journey for both our-patients and inpatients with precise medical outcome and smarter user experience (UX) across every point of care (POC) would become an even more important yet complicated task to achieve. In additions, due to the recent big success of LLM (Large Language Model) for generative AI, the dialogues among patients, doctors and nurses at the point of cares will need to be well archived as the new data type to traditional hospital dataset of EMR and medical IoT sensors. All these cannot be done independently on individual system nor device. In this talk, A simple, secure, scalable and flexible platform architecture will be proposed over Quanta QOCA to address all these challenges for smart healthcare anytime, anywhere, anyone at any age.

The implementation of artificial intelligence products: Experience in National Taiwan University Hospital

人工智慧醫療產品的落地：臺大醫院經驗

Lu-Cheng Kuo

郭律成

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臺大醫院資訊室 及 智慧醫療中心

臺大醫院 內科部

Like pharmacy and medical device, medical artificial intelligence (AI) products are strictly regulated all around world. SaMD (software as medical device) are graded into 4 categories according to the risks in clinical use.

In accordance with TFDA SaMD regulation and NTUH principles, we set up a process for the implementation of AI products. Various aspects, including intellectual property, IRB approval, integration of clinical workflow and long-term maintenance, are considered. A two-step process, test-run and formal implementation, will guarantee the accuracy and usability of the AI products.

A proposed multi-criteria optimization approach to enhance clinical outcomes evaluation for diabetes care: A commentary

以多目標優化加強糖尿病護理的臨床結果評估：一則評論

Hsing Luh

陸行

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國立政治大學 理學院應用數學系

Background: There are several challenges in diabetes care management including optimizing the currently used therapies, educating patients on self-management, and improving patient lifestyle and systematic healthcare barriers.

Methods: The discipline-free methods used in implementation science research, applied to efficiency and quality-of-care analysis are presented.

Results: The purpose of performing a systems approach to implementation science aided by artificial intelligence techniques in diabetes care is two-fold: 1) to explicate the systems approach to formulate predictive analytics that will simultaneously consider multiple input and output variables to generate an ideal decision-making solution for an optimal outcome, and 2) to incorporate contextual and ecological variations in practicing diabetes care coupled with specific health educational interventions as exogenous variables in prediction.

Conclusion: We illustrate logically formulated predictive analytics with efficiency and quality criteria included for the evaluation of behavior change intervention programs, with the time effect included, in diabetes care and research.

How instant and rapid whole-genome sequencing analysis helping clinicians and the limitations we are facing now

即時快速全基因定序於臨床之運用及其目前需要面對之相關問題

Chia-Feng Yang

楊佳鳳

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Next generation sequencing (NGS) is one of the most important tools for the development of precision medicine. It has greatly improved the ability of sequencing and has become an important tool in disease diagnosis and medication. Through the popularization and maturity of this technology, the cost of sequencing has been greatly reduced and the output of information has become faster. Meanwhile, the efficiency of analyzing huge genome sequence data in the back-end had become more and more important. Our center cooperates with a current bioinformatics service company to jointly develop a rapid diagnosis platform for whole-exon sequencing and whole-genome sequencing. The platform has a concise, user friendly and easily understand interface. This allows us to quickly upload the whole gene sequencing data and analyze according to the doctor's needs in real time. Through the development of the real-time analysis system, patients with rare genetic diseases will be able to obtain rapid diagnosis and early treatment. Moreover, if other disease-causing gene mutations were found during the analysis process, personal prevention/medical plans can be formulated for each individual's situation. We hope this system could make the analysis of WES/WGS more accessible and useable for the general physicians. However, we are still facing some limitations of WES/WGS and the ethical problems. We could think about the impact of the era of WES/WGS which could totally change the approach of our patients.

The application and perspective of artificial intelligence in retina

人工智慧在眼視網膜科的應用與願景

De-Kuang Hwang

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Background: The development of artificial intelligence (AI) and deep learning (DL) provided precise image recognition and classification in the medical field. Ophthalmology is an exceptional department to translate AI applications since non-invasive imaging is routinely used for diagnosis and monitoring.

Methods: This review discusses the current research and application of AI, telemedicine, and home monitoring devices on retinal disease.

Results: In recent years, AI-based image interpretation of optical coherence tomography (OCT) and fundus photograph in retinal diseases have been extended to diabetic retinopathy (DR), age-related macular degeneration (AMD) and other retinal diseases. The three main applications of AI in retina included diagnosing/screening and autosegmentation. Assistance of surgery has been tried in retinal field.

Conclusion: AI has already been used in the ophthalmology field nowadays. With the improvement of 5G, telemedicine and telesurgery would probably a perspective in the future.

The transferable artificial intelligent model based on electrocardiogram: A prospective observational study toward home-based application of single-lead ECG in identifying heart failure with low left ventricular ejection fraction

居家單導聯心電圖在辨識低左心室射血分數心臟衰竭方面的前瞻性研究：基於可轉移的人工智能模型

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Heart failure with reduced ejection fraction (HFrEF) is a serious condition that is often underdiagnosed, and can have significant consequences if left untreated. Although several ECG abnormalities, such as atrial fibrillation, pathological Q waves, and left ventricular hypertrophy, can be seen in HF patients, none of these findings are specific to HF. A meta-analysis of four studies including 1,419 patients using ECG for HF screening reported an AUC of only 0.84. Recently, the EAGLE trial reported that with the help of AI-enable 12-lead ECG, patients had a significantly increased diagnosis rate of HF can be screened out. However, few studies have focused on training an AI model with less ECG leads (e.g. 3-channel or single-lead ECG), since the 12-lead ECG still has limitations as an effective home-based screening tool. Furthermore, strategies for leveraging existing 12-lead ECG databases to generate transferable models with fewer leads while preserving performance have not been discussed.

In this study, we developed several CNN models from a 12-lead ECG database containing 56,479 recordings from 33,010 patients for both 3-lead and single-lead ECG inputs, and systematically compared the performances between different models. To test the transferability and clinical usability of the pretrained model in real-world scenarios, we designed a prospective pilot study using a wristband that records 30-second single-lead ECGs and a cloud system. Patients who visited cardiology outpatient clinic were asked to record and upload ECGs by themselves in the hospital. Furthermore, we incorporated heart rate variability (HRV) analysis of 30-second single-lead ECGs into the transferred model to improve screening performance.

Among all single-lead models, most models could reach AUC of 0.88-0.89, including lead aVR, lead I, lead V5, and lead V6. We chose the lead I model (MI) for operational convenience in the prospective study and showed the robustness of the model by testing it on wristband ECGs (AUC of 0.88). When the model was combined with HRV parameters, the AUC of the new model increased to 0.92 with a high sensitivity of 94% and high specificity of 81%. These results suggest that our approach has the potential to be a cost-effective and easily accessible tool for general population screening.

Maximizing health through genomic information

利用基因體資訊讓健康最大化

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Eighty percent of health problems in a person's lifetime are directly or indirectly related to genetics, especially complex diseases such as cancer, dementia, diabetes, and heart disease. These diseases are caused by genetic variations as well as acquired factors. Although genes cannot be changed, these diseases can be avoided precisely by adjusting acquired factors. Through comprehensive genomic analysis with whole exome/genome sequencing, coupled with single-gene and polygenic risk score analyses, by identifying these disease-predisposing genetic variations can be identified, the goal of personalized and prevention medicine can be achieved.

Test-fairness deep learning with influence score

基於影響分數之測驗公平的深度學習

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The prevalence of artificial intelligence has led to many significant problems that catch people's eyes. Among them, bias in AI systems is a serious problem that should be carefully addressed. The source of bias usually comes from data collection focusing on specific populations or groups. The data with bias can be used easily to produce a model with discriminatory behavior that in turn results in different prediction performances for different groups. Therefore, it is crucial to eliminate the discriminatory effect and make the model fair. To mitigate the discriminatory effect, we propose a new feature selection method based on deep learning and statistics to make the model fair and retain the prediction performance simultaneously. On top of deep learning models, we adopt the influence score (I-score), which is a statistic that takes the interaction between multiple features into consideration, in the proposed method. The influential features encoding the bias information will be selected and excluded in follow-up predictions. The fair I-score model will explore the features not associated to the discriminatory factor so that the resulting prediction performance is high. We conduct the empirical study by the ISIC 2019 and ASAN skin lesion datasets. While the ISIC 2019 dataset is related to the population in the West, and the ASAN dataset is related to the population in South Korea. As the prevalence rate of skin cancer in the West is higher than that in Asia, the area information will generate the bias for the prediction model. The empirical study shows that the fair I-score model can precisely classify the types of skin lesions by eliminating the bias information inherent in the original model.

Intelligent nursing informatics model in patient safety-centered care

以病人安全為中心之智慧科技照護模式

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The intelligent nursing informatics model at Taipei Veterans General Hospital is centered around patient safety. Since the development of the nation's first Barcode Medication Administration(BCMA) Safety Check System in 2005, the hospital has continuously built various infrastructure systems for intelligent healthcare. These systems incorporate strategies such as information integration, process reengineering, process monitoring, real-time feedback, intelligent decision-making, data analysis, and quality management. Several advanced nursing systems that have been optimized and developed can be cited as examples.

Firstly, based on the nursing process as the theoretical framework, the Nursing Information System(NIS) has been established as a nursing care plan intelligent decision support system. It combines several nursing assessment systems and health issues to provide intelligent decision support and evidence-based nursing interventions are recommended for nurses in formulating individualized care plans for patients. The discharge planning service is initiated upon three-step screening process., and suggests interdisciplinary team members and interventions, while also integrating with the Continuous Integrated Case Management System (CICMS) for continuity of care and case management. The Nursing Care Quality Improvement (NCQI) monitoring system allowing for the integration of quality improvement into daily nursing practices. The effectiveness of quality monitoring is displayed through data-driven dashboards. With patient centered safety care, a single barcode operation has been developed to ensure multi-level checks for medication administration. Process monitoring and quality management leave no errors. Lastly, through the integration of information among systems and real-time feedback, administrative management tasks, enabling efficient and agile decision-making. This patient safety-centered nursing informatics system provides healthcare team members with real-time, comprehensive, and accurate assessment information. Taipei Veterans General Hospital continues to leverage evolving information technology and pursue constant innovation, striving to achieve the vision of patient safety and nurse well-being.

The application of AI in the diagnosis of cerebrovascular diseases

智慧醫療在腦血管疾病的診斷應用

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A distinct and important risk factor for ischemic stroke among East Asians is intracranial arterial stenosis (ICAS), which affects 15–20% of the elderly population. ICAS is typically asymptomatic, which is unfortunate because most people only learn of it after a stroke. Moreover, individuals with symptomatic ICAS have an annual recurrence rate of 10 to 15%, which is significantly greater than that of patients with stroke from other etiologies. Vascular risk factors can be properly controlled to treat ICAS. Determining the presence of ICAS prior to the commencement of a stroke is crucial.

Advanced neuroimaging techniques like brain magnetic resonance angiography and computed tomography are required to detect the presence of ICAS. Yet, the ordinary public cannot afford to use these cutting-edge neuroimaging techniques in health examinations. Instead, ultrasonography is less expensive and is frequently used in medical assessment. Ultrasonography has severe limitations in finding ICAS, including a poor success rate for transcranial ultrasound and subpar diagnostic accuracy of current methods, even though it is practical for screening extracranial vascular disease.

We developed a diagnostic model from extracranial cerebral arteries using a deep learning algorithm to distinguish between patients who had and did not have ICAS. This approach offers a lot of benefits: It uses extracranial vascular ultrasound, which eliminates the issue of transcranial ultrasound's low success rate, does not require ultrasound technicians to change their work habits, and may give ICAS with sufficient diagnostic sensitivity and accuracy.

The purpose of the current speech is to share the experience of developing the ICAS diagnostic methods at National Yang Ming Chiao Tung University and Taipei Veterans General Hospital.

Advancing healthcare with AI and next generation health information system

專為未來醫療打造的次世代智慧醫療資訊平台

Miranda Wu

毋文涵

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華碩電腦股份有限公司 AICS

Along with medical regulation relaxation and technology breakthrough, most hospitals in Taiwan have been caught in a dilemma of renovating Health Information System (HIS), which in general is considered legacy because of the system complexity, data limitation, and information silo. Current HIS in use is usually composed of various subsystems of clinical, administrative, and financial managements. Since the subsystems are possibly developed in different programming languages, among which some are outdated and rarely used, the burden of integration and operations has been increased. Moreover, the data schema of HIS is originally designed for health insurance declaration. To retain more information on patient's care, data columns should be expanded, and systems require upgrades. This process can be done only if HIS is shut down temporarily. In addition to the potential cost, extra efforts are needed when integrating and utilizing data among subsystems because of the inconsistency of the data models, let along data integration among hospitals.

ASUS Next Generation Health Information System (xHIS) is a powerful AI-embedded platform that aims to give healthcare providers a modularized, hybrid cloud-based, and FHIR-enabled information service. Modularized architecture with microservices equips xHIS with smooth development and easy operation since each microservice is independently deployed and extended, causing rare influences to the others. Cloud-based platform enables compatibility, extensivity and portability. Existing HIS systems can be integrated less painfully to xHIS, which allows IT to develop patient-centric services effectively to enhance the healthcare quality. With web-based applications, each service is accessible any time, any where, and any device.

As a platform, xHIS favors internal groups to develop applications to given purposes, as well as third-party developers to launch new proprietary services. This breakthrough of medical technology will bring more momentum to this industry and complete the ecosystem.

IMU application in orthopedic

慣性感測模組於骨科手術之應用

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Background: Measurement of motion of body segments including four limbs and trunk play an important role in the management of orthopedic patient and monitoring the surgical result. Traditional approaches rely on measurements made within the laboratory, radiological or clinical environments still play a fundamental measurement. However, inertial sensors are proven to provide an opportunity to quantify these outcomes in patients' natural environments, providing greater capacity of validity usability, and also provide an opportunity to convert large data sets of movement information for the development of AI model adoption for orthopedic patients.

Methods: To demonstrate the usability of IMU (inertial measurement unit) on the orthopedic surgical patients, we apply the IMU measure in patient receiving operation for degenerative deformity spinal surgery and knee arthroplasty surgery, to develop the automatic measurement system for monitoring the patients' preoperative and postoperative range of motion in these body segments.

Results: Five cases of spinal deformity surgery patients and ten knee arthroplasty patients had enrolled in our study, the preoperative, postoperative in-hospital and 6 weeks after surgery measurement data was collected and analyzed.

Conclusion: The IMU measurement system applied in the orthopedic spine and knee surgery demonstrated to be a continuous and non-invasive tool with good prevision and mobility, and also provide the opportunity for the creative AI model adoption and utilization.

The challenges in external validation of a machine learning model: A experience sharing from ICU in TPEVGH

機器學習模型外部驗證的挑戰：臺北榮總 ICU 的經驗分享

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As the use of machine learning (ML) models becomes more widespread in various domains, the need for external validation of these models becomes increasingly critical. External validation ensures that the model can generalize to new data, making it reliable and trustworthy. However, external validation of an ML model presents significant challenges, including dataset bias, data quality, and interpretability of results. In this speech, we will explore the challenges in external validation of an ML model, including the sources of bias and data quality issues, methods for validating model performance on external datasets, and the importance of model interpretability for gaining trust in the results.

Exploration and planning of precision medicine through the integration of traditional Chinese and Western medicine in Taiwan

臺灣中西醫整合精準醫學的探索與規劃

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Background: Precision medicine is an innovative approach for better patient stratification, diagnosis and treatment that considers a person's genotype, phenotype and its influential factors. The individual's body constitution is highly stressed in traditional Chinese medicine (TCM). It assumes that the diversity of diseases manifestations along with tailored treatments in different patients with the same disease derives from differences in each patient's constitution. To take advantage of the application of TCM body constitution, we are exploring and planning of precision medicine through the integration of TCM and Modern medicine (MM) by collaboration among NRICM, Academia Sinica, and Tri-Service General Hospital.

Methods: The big database of integrating TCM and MM is composed of two sources: (1) Taiwan Biobank: this database includes interview results of Body Constitution Questionnaire (BCQ) of healthy participators, and is served as comparing baseline for the patient group. (2) Breast cancer patient's recruitment: the patients were interviewed with BCQ several times in their treatment course sequence. They were also invited to join the Taiwan Precision Medicine Initiative (TPMI). Then, their electronic health record and genotyping data were assessed. We are also testing the pulse diagnosis equipment, hoping to increase the grasp of sub-health and disease states.

Results: The big data analysis revealed that TCM body constitution measurement can be used in precision medicine to group patients. Analysis of TCM constitution score and gene analysis of different disease groups can help to find possible genes related to different constitutions.

Conclusion: Through the detection of genes, body constitutions and physiological information, people with potential disease risks can be identified. Then use health knowledge to adjust living habits, diet content, and exercise guidance to avoid frailty, and achieve the purpose of precise health care and disease treatment.

Why is FHIR TW Core IG important?

為何臺灣 FHIR 核心實作指引如此重要？

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Why does HL7 International develop the latest standard FHIR (Fast Healthcare Interoperability Resources)? There are at least three reasons. Firstly, tooling for previous HL7 standards, e.g., Clinical Document Architecture (CDA), has always been an issue. These tools generally need to be explicitly designed for HL7 and do not always provide in time. Also, there are new use cases especially involving mobile devices, where the current standards were not a good fit. Thirdly, the use of a REST-based architecture for webspace is widely used in other domains. To respond to these and other issues. FHIR is designed for easy to develop, implement, semantically robust, human-readable, validate electronically, and embed modern web-based communication technologies (HTTP, XML, JSON, etc.).

However, with the launch of TW Core IG, more and more implementers are asking what TW Core IG is. How to adopt TW Core IG? Do I have to adopt TW Core IG?

As medical data exchange within and across countries begins to be based on FHIR. If people in Taiwan want to collaborate with international organizations in (bio-)medical informatics research, sell medical information systems and applications to other countries, or purchase the most advanced medical information products abroad. In that case, can they interface with the corresponding FHIR-based medical information? Stakeholders such as researchers, physicians, IT engineers, medical institutions, and government agencies who want to adopt FHIR always ask the first question: How do we start? What is the correct adoption of FHIR?

To respond to these questions, Dr. Lee has collated her observations and learning from the past few years to provide the audience with the current international practices and the latest information. She hopes to alleviate the audience's doubts, encourage the audience to sense and accept FHIR and adopt FHIR confidently. When organizations and individuals have FHIR capability, they can develop current technical capabilities, enhance the international applicability of intelligent medical R&D artifacts and products, and maximize their qualitative and quantitative contributions.

The practice of AI in the medical clinical field: Health Examination Center in Kaohsiung Veterans General Hospital

AI 在醫療臨床場域的實踐：以高雄榮總健檢中心為例

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AI-led smart healthcare has three major goals: improve the quality of care, reduce healthcare costs and enhance the healthcare experience. The goal is to promote public health finally. Facing the era of AI big data, how to create valuable decision through a large amount of high-speed and diversified information by an innovative intelligent engine is a major challenge. However, opening-up the medical field and introducing the elements of smart healthcare can bring many benefits. For health examination centers, we must also move from traditional digitalization to intelligence in the AI era.

The Health Examination Center in Kaohsiung Veterans General Hospital is committed to a new cross-disciplinary health check-up experience. Through the introduction of AI smart medical capabilities, the traditional health examination service model will be transformed to a smart one. For example, the introduction of intelligent positioning and scheduling system create an intelligent field and make the process more efficient. Introduce intelligent health risk assessment to maximize the benefits of health check-up. In addition, the health examination report and education information are presented in the form of audio and video, overcoming the obstacles of traditional paper reports. Finally, a standardized intelligent medical information exchange platform is established to overcome the limitations of information grafting and create a health management platform after health examination. Through these AI smart medical capabilities, the purpose of intelligent health examination is realized, and the greatest value of health checkers is created.

Prediction of the development of acute kidney injury following cardiac surgery by machine learning

運用人工智慧預測心臟手術後急性腎損傷

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Background: Cardiac surgery-associated acute kidney injury (CSA-AKI) is a major complication that results in increased morbidity and mortality after cardiac surgery. Most established prediction models are limited to the analysis of nonlinear relationships and fail to fully consider intraoperative variables, which represent the acute response to surgery. Therefore, this study utilized an artificial intelligence-based machine learning approach thorough perioperative data-driven learning to predict CSA-AKI.

Methods: A total of 671 patients undergoing cardiac surgery from August 2016 to August 2018 were enrolled. AKI following cardiac surgery was defined according to criteria from Kidney Disease: Improving Global Outcomes (KDIGO). The variables used for analysis included demographic characteristics, clinical condition, preoperative biochemistry data, preoperative medication, and intraoperative variables such as time-series hemodynamic changes. The machine learning methods used included logistic regression, support vector machine (SVM), random forest (RF), extreme gradient boosting (XGboost), and ensemble (RF + XGboost). The performance of these models was evaluated using the area under the receiver operating characteristic curve (AUC). We also utilized SHapley Additive exPlanation (SHAP) values to explain the prediction model.

Results: Development of CSA-AKI was noted in 163 patients (24.3%) during the first postoperative week. Regarding the efficacy of the single model that most accurately predicted the outcome, RF exhibited the greatest AUC (0.839, 95% confidence interval [CI] 0.772-0.898), whereas the AUC (0.843, 95% CI 0.778-0.899) of ensemble model (RF + XGboost) was even greater than that of the RF model alone. The top 3 most influential features in the RF importance matrix plot were intraoperative urine output, units of packed red blood cells (pRBCs) transfused during surgery, and preoperative hemoglobin level. The SHAP summary plot was used to illustrate the positive or negative effects of the top 20 features attributed to the RF. We also used the SHAP dependence plot to explain how a single feature affects the output of the RF prediction model.

Conclusion: In this study, machine learning methods were successfully established to predict CSA-AKI, which determines risks following cardiac surgery, enabling the optimization of postoperative treatment strategies to minimize the postoperative complications following cardiac surgeries.

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小兒麻醉的現況與進展

Pediatric Anesthesia: Current Situation and Update

時 間：112年7月8日 08:20~12:25

Time：July 8, 2023 08:20~12:25

地 點：臺北榮民總醫院 中正樓14樓 胸腔部會議室

Place：14F, The Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

小兒麻醉的現況與進展

Pediatric Anesthesia: Current Situation and Update

Anesthesia for “bedside” preterm patent ductus arteriosus ligation

早產兒床邊開放性動脈導管結紮麻醉

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The fetal ductus arteriosus (DA) diverts cardiac output away from the lungs toward the placenta to support fetal systemic oxygenation. After delivery, circulatory adaptation depends on DA closure within the first days of life. However, DA closure fails to occur frequently in preterm infants because of immature structures and responses to constrictive mechanisms. A persistent patent ductus arteriosus (PDA) occurs in approximately 1 in 2,500 to 1 in 5,000 live births, and exceeds 50% in preterm infants ≦ 28 weeks' gestational age. The clinical consequences in preterm infants with PDA include increased pulmonary blood flow, increased the risk of hemorrhagic pulmonary edema, and ductal steal from the systemic circulation. These systemic hypoperfusion may be associated with necrotizing enterocolitis, and intracranial hemorrhage.

In premature infants, initial management of a PDA is typically pharmacological closure using prostaglandin inhibitors such as ibuprofen or indomethacin. Surgical ligation is usually reserved for patients who fail medical therapy and can be undertaken either in the operating room (OR) or in the neonatal intensive care unit (NICU). Anesthetic management for PDA ligation in NICU (“Bedside” PDA ligation) faces the challenges not only in performing a surgical intervention outside the OR but in caring the fragile and sick preterm newborns.

Perioperative concerns for bedside PDA ligation in preterm infants include temperature, vascular access, airway and ventilation issues, anesthetic agents, infection concerns and post-ligation hemodynamic management (such as postligation cardiac syndrome). In addition, ligation of the ductus arteriosus is a multidisciplinary team effort that should involve in well communication between the surgery, anesthesiology, cardiology, and neonatology. We have started the “bedside” PDA ligation in NICU since 2019, and the experience shows that the anesthesia and surgical procedure are feasible and safe to avoid the risks of transport, need for ventilator changes, and hypothermic exposure.

An overview for non-cardiac pediatric thoracic anesthesia

小兒胸腔手術麻醉

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Children presenting for thoracic surgery are a heterogenous group of patients who pose a variety of challenges to the anesthetic care team. A thorough understanding of the pediatric patient, including development changes in cardiopulmonary anatomy and physiology, and the implications of surgical lesions and interventions is essential in order to provide safe and effective clinical care.

I reviewed four most common lung disease in neonate and infant, including congenital diaphragm hernia, trachea-esophageal fistula, congenital pulmonary airway malformation, and pulmonary sequestration. The specific pathophysiology and their common comorbidities complicate the process of anesthetic care.

With the improvement in surgical technique, minimally invasive approach was getting popular in pediatric population. To accomplish successful thoracoscopic surgery, we need to have successful one-lung ventilation. The device and technique is similar but not exactly the same as in adult population.

The provision of safe and effective anesthetic care during thoracic surgery in children necessitates a thorough understanding of the fundamental principles of both pediatric and thoracic anesthesia.

Single-center experience and evidence update on anesthesia care for pediatric scoliosis surgery

兒童脊椎側彎手術麻醉照護之經驗分享與實證更新

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Scoliosis is a common disease in juvenile and adolescent populations with an overall prevalence of 0.5 to 5.2 % reported by the current school screening studies. Scoliosis is an abnormal curvature of the spine, which may progress rapidly during periods of adolescent physical growth and can impair cardiorespiratory function in severe cases. Untreated scoliosis may lead to severe cardiopulmonary complications, and curves of ≥ 30° tend to deteriorate and necessitate a surgical intervention. Surgical management of scoliosis is most frequently performed with posterior spinal fusion in conjunction with skull femoral traction. Scoliosis poses a high risk of anesthesia, including surgical hemorrhage, postoperative uncontrolled pain, and spinal cord injury.

Despite the advances in surgical and anesthetic techniques, patients have a high risk of massive bleeding and a need for blood transfusion during scoliosis correction surgery. Recent studies have reported several feasible strategies to reduce surgical blood loss in pediatric scoliosis surgery, including high-dose tranexamic acid infusions and deliberate hypotension. Furthermore, posterior spinal instrumentation with traction for scoliosis involves extensive surgical incision and massive tissue trauma, which may induce severe acute pain. Intravenous opioid-based analgesia has been the mainstay of analgesic modality for these patients. Nevertheless, the adverse effects of systemic opioids may limit the analgesic efficacy and cause undertreated pain after scoliosis surgery. Multimodal analgesia is a widespread therapy to reduce the dose of opioid and thereafter its adverse effects after scoliosis surgery. In the recent decade, dexmedetomidine has been increasingly used as a non-opioid adjuvant analgesic in multimodal analgesic regimen to improve postoperative pain control while decreasing opioid-related side effects.

We will review the current literature on the perioperative anesthesia management in pediatric scoliosis correction surgery, which will particularly focus on intraoperative hemodynamic management and perioperative analgesia. In addition, we will also share our teamwork experience in Taipei Veterans General Hospital to clearly delineate the efficacy of clinical strategies in reducing intraoperative bleeding and acute pain. We will also describe the anesthesia care protocol and systemic hemodynamic goal to maintain neurophysiological monitoring signals and to prevent neurological injury during scoliosis correction surgery.

Perioperative care for pediatric liver transplant in Taipei Veterans General Hospital: Experience sharing and future development

台北榮民總醫院小兒肝臟移植術中照顧經驗分享與未來展望

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Pediatric liver transplant is a complex procedure which needs seamless integration of many clinical specialties. Here we presented our experience in pediatric liver recipients' perioperative care. After pediatric surgeons initiated the pre-liver transplant evaluation, anesthesiologists joined the meeting weekly. For perioperative care, we could roughly divide our small patients into two groups, with or without portal hypertension.

For those without portal hypertension, the indication for liver transplant was mostly genetic/metabolic disease of liver. After the enrollment of evaluation, our Pediatric Gene and Endocrinology doctors would thoroughly investigate genetic mutations to identify the subtype that would benefit from liver transplant. Another important consideration was development milestones. It was really a tough decision to receive liver transplant or not, for parents, when such diseases caused developmental delay. Patients of biliary atresia after Kasai procedure were common in pediatric liver transplant with portal hypertension.

Collateral circulation developed commonly in portal hypertension. After all life will find a way. Considering the small body size of our recipients, hepatic and portal vein anastomoses were done with total clamp. Therefore it was usually easier to maintain hemodynamic stability in pediatric liver recipients with portal hypertension. However, after reperfusion, it would also be a challenge for the transplant team to restore the adequate portal perfusion.

In the foreseeing future, we looked forward to expand our multi-model pain management into pediatric liver recipients' postoperative care. Of notice, long term care for these vulnerable children were really hard work. To my deepest regret, some gave rise to a broken family. Looking back at the 17 past years, I am really thankful to everyone who has been part of my journey in liver recipient's perioperative care, and I do hope these kids grow up in a family full of love.

Regional anesthesia in pediatric surgery

小兒區域麻醉的進展

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Regional anesthesia in pediatric surgery has gained acceptance and popularity worldwide over the past few decades, however has not yet popularized in Taiwan. There is good evidence that regional anesthesia provides good-quality postoperative pain relief, also advances in ultrasound technology have facilitated practice of regional anesthesia in pediatric practice.

In this talk, I will discuss the benefits and safety of regional anesthesia, safety in children. I will also discuss differences of anatomy, ultrasound imaging, and local anesthetics dose between adult and children. Finally, how regional anesthesia in pediatric surgery is performed in Taipei Veterans General hospital will be discussed.

Non-operating room anesthesia for pediatric MRI: VGH experience

手術室外之兒童核磁造影麻醉：北榮經驗

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鄭宏煒

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Non-Operating Room Anesthesia (NORA) has become a widely accepted practice for pediatric patients undergoing diagnostic procedures, such as MRI. However, due to the loud noise and enclosed space of the MRI scanner, many children may feel anxious and uncooperative during the procedure. Therefore, moderate sedation is commonly used during pediatric MRI scans to ensure patient comfort and good image quality.

Selecting sedative agents and techniques is crucial in ensuring successful airway management during MRI. We will discuss the advantages and disadvantages of various sedative agents commonly used for pediatric MRI sedation, including propofol, barbiturate, midazolam, and ketamine. Propofol is a short-acting intravenous sedative-hypnotic agent that provides rapid and predictable sedation. Propofol is commonly used for pediatric MRI sedation due to its rapid onset, quick recovery, and minimal side effects. However, it can cause respiratory depression and requires careful titration to maintain airway patency. Ketamine is a dissociative anesthetic agent that provides sedation, analgesia, and amnesia. It has a rapid onset of action and is administered via intravenous or intramuscular injection. It preserves airway reflexes and can be used in children with difficult airways or those requiring prolonged sedation.

The pediatric airway differs from the adult airway in many ways, including size, shape, and function. It is smaller and more flexible than the adult airway, making it more prone to obstruction and challenging to manage. Careful patient selection is essential for successful airway management during MRI sedation. Children with a history of airway obstruction, obstructive sleep apnea, or difficult airways should be evaluated carefully before sedation. In addition, continuous monitoring of the patient's respiratory rate, oxygen saturation, end-tidal CO2, and heart rate is essential during MRI sedation to detect and manage adverse events.

Effective airway management during MRI sedation is essential for pediatric patients. Various sedative agents, patient selection, and continuous monitoring are crucial for successful airway management during MRI. Alternative airway management strategies, such as supraglottic airways, may sometimes be required. We will also share the VGH experience for anesthesia providers managing the pediatric airway during MRI scans in non-operating room settings.

Pediatric dental intravenous sedation. Experiences of Stardust anesthesia specialists

訢辰麻醉鎮靜團隊的兒童牙科鎮靜經驗

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Treatment of complex dental carries in children is challenging without the aid of sedation or anesthesia. Several methods, such as oral sedation, nitrous sedation, intravenous sedation and general anesthesia are the traditional candidates.

Stardust Anesthesia Specialists started to build up a dental clinic-based intravenous sedation program since 10 years ago. At the time of the lecture, more than 14000 kids had their carries treated under intravenous sedation.

Intravenous catheter placement in kids can be difficult. Sedative premedication can be helpful. More than 90% of kids receive oral sedatives, while less than 5% requires direct intranasal spray or intramuscular injection of sedatives. If nitrous is available, it is also a good tool to speed up intravenous catheter placement.

Several main problems can be encountered during dental intravenous sedation. Treatment over the lower teeth requires a downward force over the mandible, which can cause airway depression. Intravenous sedative medicines can cause respiratory depression which requires careful titration. Water during dental treatment is a nightmare and may lead to devastating disasters such as aspiration and laryngospasm.

Pediatric dental intravenous sedation requires the personal of multi-subspecialties. Anesthesiologists and dentists should be familiar with the fundamental knowledge of both sides. Communication throughout the treatment is the key of safety and fluency of the procedure.

Utilizing modern technology has improved the safety of pediatric intravenous dental sedation. Capnography and pretracheal sedation stethoscopes are very helpful in the early detection of respiratory change, laryngospasm and aspiration. Density spectral array provides precise information of sedation depth which can lead to early ambulation and decrease of post-anesthesia side effects.

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國內醫用迴旋加速器的建置與發展

Construction and Development of Medical Cyclotron in Taiwan

時　間：112年7月8日　08:15~12:00

Time：July 8, 2023　08:15~12:00

地　點：臺北榮民總醫院 第三門診9樓創新沙龍

Place：The Clinical Innovation Center, Taipei Veterans General Hospital

國內醫用迴旋加速器的建置與發展

Construction and Development of Medical Cyclotron in Taiwan

Experiences in radiation medicine and risk communication for recovery of the community in Fukushima after a nuclear disaster

福島核電廠意外後，輻傷救護、社區復原與溝通之經驗分享

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The Great East Japan Earthquake and Nuclear Disaster Memorial Museum, Fukushima, Japan
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Twelve years have passed since the accident at the Fukushima Daiichi Nuclear Power Station (FDNPS) in 2011. Since then, we have been assisting in reconstruction efforts for Kawauchi Village, Fukushima Prefecture, which was the first village to declare that residents could return to their hometown. In April 2013, Nagasaki University and the Kawauchi Government Office finalized an agreement of cooperation for reconstruction of the village. The university began comprehensive support for residents of the towns of Tomioka, Ohkuma, and Futaba in 2016, 2020, and 2021, respectively. Twelve years after the accident, gaps in the recovery process are apparent in all municipalities surrounding the FDNPS. After a nuclear disaster, radiation medical science experts need to fully understand the situation in each municipality in order to contribute most effectively to recovery.

Development of prostate-specific membrane antigen-targeted radiopharmaceuticals for diagnosis and therapy of prostate cancer at BC Cancer

溫哥華 BC Cancer 在 PSMA 核醫藥物的研發經驗

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Background: Prostate-specific membrane antigen (PSMA)-targeted radiotherapeutic agents have been widely used in the clinic to treat metastatic prostate cancer. However, their off-target uptake in kidneys and salivary glands poses a toxicity concern and can severely affect quality of life for survivors. Recently we observed in a mouse model that monosodium glutamate pretreatment reduced uptake of ^{68}Ga-PSMA-11 in salivary glands and kidneys but had no effect on tumor uptake (Rousseau E, et al. J Nucl Med 2018; 59: 1865). This suggests that the Glu motif in the widely used Lys-urea-Glu pharmacophore might mediate the off-target uptake of PSMA-targeted radioligands.

Methods: In this study, we investigated the effects of replacing Glu in the PSMA-targeted Lys-urea-Glu pharmacophore with a close analog on the uptake of kidneys, salivary glands and PSMA-expressing LNCaP tumor xenografts. New derivatives obtained by replacing Glu with Aad (2-aminoadipic acid), Cmc (S-carboxymethylcysteine), Cms (O-carboxymethylserine), or 4-F-Glu were synthesized and radiolabeled with ^{68}Ga or ^{18}F for positron emission tomography imaging in mice bearing LNCaP tumor xenografts.

Results: Compared with radioligands derived from the Lys-urea-Glu pharmacophore, the PSMA ligands derived from Lys-urea-Aad, Lys-urea-Cmc, Lys-urea-Cms and Lys-urea-4-F-Glu showed comparable uptake values in tumors but much lower uptake values in kidneys and salivary glands.

Conclusion: Our data suggest that replacing Glu in the widely used PSMA-targeted Lys-urea-Glu pharmacophore with a close analog can greatly reduce the off-target uptake in kidneys and salivary glands. The new pharmacophores, Lys-urea-Aad, Lys-urea-Cmc, Lys-urea-Cms and Lys-urea-4-F-Glu, are promising for the design of PSMA-targeted radioligands especially for radiotherapeutic agents to minimize toxicity to kidneys and salivary glands.

Developments of PET radiopharmaceuticals for imaging prostate cancer

攝護腺癌正子檢查製劑之發展

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Prostate cancer is the most common cancer diagnosis in men and a leading cause of cancer-related morbidity and mortality. Novel radiopharmaceuticals such as ^{18}F-fluciclovine and choline PET have been used increasingly in the biochemical recurrence (BCR) setting with limited specificity. The increasing use of radiopharmaceuticals that target the prostate-specific membrane antigen (PSMA) is based on growing scientific evidence that supports their favorable imaging performance. Many PSMA-targeted imaging agents are being evaluated, and two are currently approved by the Food and Drug Administration, USA: ^{18}F-DCFPyL and ^{68}Ga-PSMA-11. Other tracers are being evaluated in phase III trials, including ^{18}F-PSMA-1007, ^{18}F-rhPSMA-7.3, ^{18}F-CTT1057, ^{68}Ga-PSMA-R2, and ^{64}Cu-SAR-bisPSMA. This presentation reviews the developments of these PET tracers particularly in radiochemical and industrial concerns.

PET radiopharmaceutical in TVGH: Retrospect and prospect

北榮正子藥物的供應及未來規劃

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The National PET/Cyclotron Center (NPCC) of Taipei Veterans General Hospital (TVGH) was completed at the end of 1992 and run by the Nuclear Medicine Department. The facility continues a long legacy of radiochemistry work that started in 1993 with the installation of the first medical base cyclotron in Taiwan, a Scanditronix MC17. The machine has proton source and is currently outfitted with 5 targets (^{18}F-, ^{18}F2, ^{11}C, ^{13}N and ^{15}O).

NPCC has two missions: a clinical production laboratory where the radiopharmaceuticals used in routine diagnostic scans, and a clinical studies production for research. NPCC produce F-18 FDG, F-18 NaF, N-13 NH3 and C-11 sodium acetate for clinical used (TFDA approved). NPCC also produce F-18 PSMA1007, F-18 FEPPA, F-18 Fallypride, F-18 FHBG, F-18 FAHA and C-11 PIB for human clinical trials.

The clinical production laboratory is operated under cGMP regulation. The facility currently has two dispensing isolator, four mini hot cells. Two of the mini hot cells house two NEPTIS boxes (mosaic-RS and perform) that are dedicated to daily F-18 FDG production. In addition, there are two Eckert & Ziegler synthesis modules for nucleophilic fluorination and C-11 label radiopharmaceuticals (C-11 sodium acetate).

Scanditronix MC17 was used almost 30 years, some component of the cyclotron maybe hard to get for maintenance. That machine is not able to production new isotope (ex. Ga-68, Cu-64 and Zr-89) for current radiopharmaceuticals.

In the future, we will setup new cyclotron for several isotope production (ex. Ga-68, Cu-64 and Zr-89). Moreover, some prospects of research and development of radiopharmaceuticals in the near future are discussed.

Current status and future prospects of nuclear medicine research and development at INER

核能研究所核醫藥物研發現況與未來展望

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樊修秀

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行政院原子能委員會核能研究所 同位素應用組

With the advent of the era of precision medicine, diagnostic and therapeutic molecular imaging technology or drugs play an indispensable role. The Institute of Nuclear Energy Research (INER) has been committed to the research of nuclear medicine and the development of imaging technology for many years. In addition to having a one-stop nuclear medicine development industry chain (from innovative research to commercialization), it is more active in line with the global trend of precision medicine development, launching a new generation of cyclotron construction plan.

So far, special achievements include: (1) Stable supply of "INER Thallium Chloride (Thallium-201) Injection" for routine clinical use. (2) Completion of pre-clinical biological research, establishment of automatic synthesis process production system and 3 batches of trial production of "Long-acting Nuclear Medicine Lu-177-PSMA INER-56 Targeted Therapy for Prostate Cancer", (3) Extended the drug stability of "I-123-MIBG injection" to 10 hours (originally 6 hours), and was approved by TFDA on May 24, 2011, and officially supplied to hospitals for academic clinical trials. (4) Continuing to implement the phase II clinical trial of "INER DOLACGA imaging agent for Liver Function", because it has excellent liver target properties and can be used to evaluate liver function and liver disease progression. (5) Taiwan's first "Carbon-14 Label Metabolism Platform" has obtained GLP certification and TFDA registration, which can accelerate the development and marketing of new drugs in the domestic industry, academia and medical circles. (6) The "*In vivo* Molecular Imaging" and "Biodistribution" test items of the "Molecular Imaging and Radiopharmacology Laboratory" have passed TAF ISO/IEC 17025 certification. (7) The only "Radiation Toxicology Laboratory" in Taiwan that has passed GLP certification, providing certified quality and safety data to accelerate the development of new nuclear medicine drugs. (8) "National Neutron and Proton Science Applied Research - 70 MeV Medium Cyclotron Construction Project", a four-year project (2023-2026), was approved by the Executive Yuan on October 21, 2010, and it has been officially launched and implemented this year.

Finally, INER looks forward to working hand in hand with the industry-university-research-medicine community in the future to march towards a new era of precision medicine in nuclear medicine.

Cross-border thinking in precision medicine: Taiwan radiopharmaceutical R&D from academia to industry

精準醫療之跨界思考：從產業界看台灣放射新藥開發

Ya-Yao Huang

黃雅瑤

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普瑞默生物科技股份有限公司

In order to create a new future for Taiwan healthcare with radiopharmaceuticals that we know much, I was founded Primo Biotechnology (Primo) in 2021. The vision of Primo is to facilitate the accessibility of novel RPs to advance Taiwan healthcare. With a full line of radiochemistry systems and PIC/S GMP-compliant manufacturing to supply novel agents for diagnosis and therapy, Primo will dedicated to deliver the next generation of personalized and precision healthcare solutions to help people in need, especially the emerging therapeutic strategy, radioligand therapy (RLT). In this talk, the different thinking working in an academic institution and a pharmaceutical company about radiopharmaceutical development will be shared via personal 20-year R&D journey and recent career change.

In addition, Asia has been a rising player in terms of economic development and so the status of Asia radiopharmaceutical market does. However, due to various barriers such as the geographical environment and transportation, Asian countries encounter challenges in information exchange and medicine delivery, not to mention differences in language, cultures, and regulations. Not only for radiopharmaceutical market, but the development of novel radiopharmaceuticals in Asia still faces considerable levels of difficulty and challenges to overcome. Taiwan has been recently regarded as an important base in Asia-Pacific economic tactics and Taiwan will be highly potential to be a great model to overcome these existing challenges through building a unique Taiwan academia-industry collaborative model. Consequently, based on personal observation for the current status of Taiwan hospitals and radiopharmaceutical companies, several trends of Taiwan radiopharmaceutical development will be suggested and Taiwan academia-industry collaborative models for radiopharmaceutical development also will be proposed, which may will be a win-win key for Taiwan healthcare.

Challenges in the production and supply chain of nuclear medicine

核醫藥物生產及供應鏈的挑戰

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Nuclear medicine is not only a drug management, but also category a radioactive substance, which can be described as the blessing of double regulations. The level of regulatory supervision is probably incomparable except for weapons and ammunition. The direct competent authorities include the Ministry of Health and Welfare(TFDA) and the Atomic Energy Council at the central level, and local health bureaus and environmental protection bureaus at the local level. Under the current PIC/S GMP standard, other raw materials other than the main ingredients must have GMP certification in addition of Certificate of Analysis. Various quality control operations in the pharmaceutical production process also include various validation operations. The finished pharmaceutical product still needs to comply with the GDP delivery specification. From the core indicators of GMP pharmaceutical factories: air flow, water flow, material flow and human flow, to the final industrial waste treatment with or without radiation, all aspects are different from ordinary drugs.

Because it is a radiopharmaceutical, it is a competition with time and cost from the qualification of the direct front-line production personnel to the qualification of the transport personnel, the use of equipment, half-life, and road supervision. Medical institutions that are end-users are also subject to dual regulations, and they also have various issues such as compliance personnel, exposure, equipment costs, and operating costs.

In detail, there are at least 50 regulations and orders layered on the nuclear medicine pharmaceutical industry and nuclear medicine department. Under the premise of abiding by laws and regulations, nuclear medicine has technical thresholds and cost thresholds that cannot be compared with other departments.

Today we are going to talk about how the nuclear medicine pharmaceutical industry and the clinical nuclear medicine team can improve the accessibility of nuclear medicine in various difficulties.

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職業病診治的新局及挑戰

The New Challenge in the Practice of Occupational Medicine

時　間：112年7月8日　08:00~12:15

Time：July 8, 2023　08:00~12:15

地　點：臺北榮民總醫院 第三門診9樓創意谷

Place：The Clinical Innovation Center, Taipei Veterans General Hospital

職業病診治的新局及挑戰

The New Challenge in the Practice of Occupational Medicine

The challenge to identify the biohazardous occupational disease of the Labor Occupational Accident Insurance: COVID-19 as an example

職災保險認定生物性危害職業病的挑戰：以嚴重特殊傳染性肺炎 (COVID-19) 為例

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吳政龍

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Occupational medicine physicians in Taiwan are used to applied the five criteria when diagnosing occupational diseases: disease diagnosis, epidemiological data, personal occupational exposure, temporal relationship between exposure and disease, and exclusion of other non-occupational causes. When examining cases, the Taiwan Labor Insurance Bureau refers to the recognition guidelines published by the Occupational Safety and Health Administration (OSHA). In 2020, Taiwan experienced a severe outbreak of COVID-19. In August 2022, OSHA released the first edition of "Recognition Guidelines for Determining COVID-19 Infection Caused by Occupational Factors." However, the aforementioned criteria or guidelines can be challenging to apply clinically.

To improve the guidelines' clinical applicability, the Taiwan Environmental and Occupational Medicine Association was commissioned by OSHA to revise them. After conducting literature reviews and expert discussions, the revised guidelines were announced in January 2023. This article aims to report on the results of the literature reviews conducted during the revision process and compare and explain the differences between the two versions, such as the standards for rebuttable presumption, the diagnose definition and the exclusion of community acquired infections.

We will discuss the challenges that physicians may encounter when diagnosing occupational diseases caused by biological hazards, such as insufficient epidemiological data, changing risk levels among occupational groups over time, changing definitions of disease diagnosis, and difficulty in distinguishing personal occupational and non-occupational exposures. Additionally, we will also discuss the effects of the overlap between the "Communicable Disease Control Act" and "Labor Occupational Accident Insurance and Protection Act" and the stigma associated with occupational diseases. Finally, we will propose strategies for addressing these challenges.

Occupational diseases that are hard to diagnose: Clinical experiences of Taipei Veterans General Hospital

困難診斷的職業病：臺北榮民總醫院經驗

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Occupational diseases are illnesses that are associated with a particular occupation or industry and result from a variety of biological, chemical, physical, and psychological hazards in the workplace. They are preventable if hazards in the workplace are eliminated or controlled. Occupational diseases span a broad range of human illnesses, many of which clinically and pathologically are not different from those of non-occupational origins. Therefore, occupational diseases may be difficult to diagnose and under-recognized. Diagnosis is complicated by the long latency typical between an occupational exposure and the appearance of illness. Further, some diseases are difficult to link to occupational exposures (e.g. cardiovascular and psychological diseases).

The occupational history is the principal clinical instrument for the diagnosis of occupational disease. The causal relationship between work and disease is established on the basis of clinical and pathological data, occupational background and job analysis, identification and evaluation of occupational risk factors and of the role of other risk factors. Failing to consider the workplace factors that may contribute to a patient's condition can result in the ordering of unnecessary tests, inappropriate referrals, and a missed opportunity to protect others who may be at risk.

Diagnosis and certification of occupational diseases is a statutory responsibility of all regional Center for prevention and treatment of occupational injury and disease. The clinical experience of hard-to diagnoses occupational diseases in Taipei Veterans General Hospital will be presented and discussed. The case studies of diagnosis of work-relatedness will serve as examples and suggestion for the physicians and occupational health professionals.

Difficulties and challenges in return to work among occupational accident workers through holistic approach

全人照護運用於職災勞工配復工的困難與挑戰

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Levels of disability and health-related work absence continue to increase, especially in workers with occupational accidents. Difficulties in return to work may increase disability and work absence. Potential factors related to return to work include health problems, personal factors, psychological factors, and social context. Physicians approach this issue through several models. First, the common and traditional model is the medical model, which mainly focused on disease and treatment, and may neglect the patient quality and subjective experiences. Second, the biopsychosocial model, which is an interactive, individual-centered approach, is suggested by current evidence on the return to work program. This model is one of the holistic models and considers person, health problems, social and occupational context.

Labor Occupational Accident Insurance and Protection Act was announced by the Ministry of Labor on 2021.04.30. Although Article 66 of the Act stipulates that employers or occupational accident workers may file applications with medical staff to help them prepare the return to work program, Article 67 stipulates that after occupational accident workers had completed medical care, the employers shall follow the return to work program to assist with the reinstatement of work. It is challenging to merge the two concepts of the Article and the principle of early intervention. Therefore, the difficulties and challenges in return to work among occupational accident workers will be presented in the speech. They may be divided into three dimensions: bio-, psycho-, and social, and involve expectations, behaviors, and social interactions. The following sections related to the biopsychosocial model will also be indicated: (1) the key elements of the biopsychosocial model on return to work; (2) why early intervention is important for difficulties in return to work; (3) strike the right balance between effective care and best social and occupational outcome; (4) successful rehabilitation program on return to work.

Finally, the experience of the ‘fit note’ in the UK will be presented, which was designed to switch the focus to what workers are capable of doing, rather than signing patients ‘off sick’ altogether. We will also discuss the possibility of implementing the ‘fit note’ in the department of occupational medicine through teamwork.

Emerging occupational diseases from indium and artificial stones

新興職業疾病：以銦與人造石為例

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Occupational lung diseases have become a growing concern not only due to past exposure to hazardous substances, but also due to the increasing possibility of exposure to indium among workers handling touchscreens and displays. Recent research has shown that the long half-life of this element's compounds in the human body can cause serious harm to health. Additionally, engineered stone has gained popularity in construction and interior design, and some reported cases suggest that workers exposed to this material may experience more severe and rapid lung diseases than those exposed to traditional stone. This course aims to address these two hazards by presenting case reports, summarizing epidemiological data from around the world, and sharing investigative and research strategies related to emerging occupational diseases.

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神經血管疾病的新進展：
影像診斷與介入治療

Update of Neurovascular Diseases: From Imaging Diagnosis to Interventional Management

時 間：112年7月8日 08:20~12:00

Time：July 8, 2023 08:20~12:00

地 點：臺北榮民總醫院 長青樓護理館會議室

Place：Nursing Arts Laboratory, Evergreen Building
Taipei Veterans General Hospital

神經血管疾病的新進展：影像診斷與介入治療

Update of Neurovascular Diseases: From Imaging Diagnosis to Interventional Management

Application of stent-graft to treat post-irradiated carotid blowout syndrome

覆膜支架於放射治療後頸動脈爆裂症候群之應用

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Carotid blowout syndrome (CBS), defined as ruptured carotid artery and its branches, is a notorious condition encountered in patients with head and neck cancer (HNC). Among all the risk factors, radiation contributes most and could increase the risk of CBS by 7.6-fold. Without timely management, post-irradiated CBS (PIRCBS) can be very fatal.

Surgical intervention of PIRCBS is associated with mortality up to 60% while neurological deficit rate up to 40%. Nowadays, endovascular intervention has been proved with good efficacy. Although the good efficacy of endovascular treatment of PIRCBS of patients of HNC, previous studies showed that deconstructive management (DE) with permanent embolization of the diseased carotid artery was associated with significantly better outcome than reconstructive management (RE) with stent-graft. More recurrent PIRCBS was noted in RE than in DE. Despite less periprocedural stroke, RE had more delayed complication such as in-stent thrombosis and septic thrombosis with brain abscess.

However, there are several benefits for PIRCBS to take RE as their prior therapeutic strategy under certain circumstances. First, if PIRCBS involved bilateral neck regions, it was not suitable to sacrifice both carotid arteries. RE is able to get hemostasis with preservation of the involved carotid arteries. Second, using RE as the prior strategy of PIRCBS does not rely on BOT result. False negative rate of BOT in severe hypotensive patients could be as high as 20%. Bypassing BOT not only saved time in management of emergency but also avoided uncommon but potential complication of BOT. Last but not least, RE can provide clinician more treatment options and enhance the surgical safety under successful stent-graft protection and also provided better quality of care for end-stage patients.

The technique of performing stent graft placement in PIRCBS and device of stent-graft itself have been improving in recent years. In our institute, the application of stent-graft in PIRCBS had played a large role and we also found some different results. The experience of Taipei Veterans General Hospital would be demonstrated in this presentation.

Endovascular treatment of post-irradiated stenosis of subclavian artery & vertebral artery

放射線治療後之鎖骨下動脈及椎動脈狹窄之血管內介入治療

Chun-Chao Huang

黃俊肇

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Background: Radiotherapy is a main therapeutic strategy of head, neck and chest cancers (HNCC) but might be associated with post-irradiated stenosis of the subclavian artery (PISSA) or vertebral artery (PISVA). The efficacy of percutaneous transluminal angioplasty and stenting (PTAS) in patients with severe PISSA or PISVA is not yet well-clarified. This retrospective study aims to evaluate the technical safety and outcomes of PTAS of severe PISSA or PISVA (RT group) and to compare with their radiation-naïve counterparts (Non-RT group).

Methods: Between 2000 and 2021, we recruited patients of severe symptomatic stenosis of the SA or VA accepted PTAS. We compared the periprocedural neurological complications, new recent vertebrobasilar ischemic lesions (NRVBIL) on diffusion-weight imaging (DWI) of postprocedural brain MRI in 24 hours, symptom relief, and long-term stent patency between the RT group and Non-RT group.

Results: For the SA, as compared with the Non-RT group (44 cases, 44 lesions), the RT group (17 cases, 18 lesions) had significantly less hypertension (58.8% vs 93.2%, p=0.003), longer stenosis (22.1mm vs 11.1mm, p=0.003), more ulcerative plaques (38.9% vs 9.1%, p=0.010) and more distal segment stenosis (p<0.001). The technical safety and outcome between the Non-RT group vs the RT group were: 1) periprocedural NRVBIL: 30.0% vs 23.1%, p=0.727; 2) symptom recurrence rate (follow-up duration: 67.1±50.0 months): 4.5% vs 11.8%, p=0.308; 3) significant in-stent restenosis (>50%) rate: 4.5% vs 11.1%, p=0.573. For the VA, as compared with the Non-RT group (22 cases, 24 lesions), the RT group (10 cases, 10 lesions) was younger (62.0±8.6 vs 72.4±9.7 years, P=0.006) and less frequently had hypertension (40.0% vs 86.4%, p=0.013) and diabetes mellitus (10.0% vs 54.6%, p=0.024). The technical safety and outcome between the Non-RT group vs the RT group were: 1) periprocedural NRVBIL: 37.5% vs 35.7%, p=1.000; 2) symptom recurrence rate (follow-up duration: 72.1±58.7 months): 0.0% vs 4.6 %, p=1.000; 3) significant in-stent restenosis (>50%) rate: 10.0% vs 12.5%, p=1.000.

Conclusion: PTAS of severe medically refractory PISSA or PISVA is effective in the management of vertebrobasilar ischemic symptoms in HNCC patients. Technical safety and outcome of the procedure were like those features in radiation-naïve patients.

Application of drug-eluting balloon to prevent in-stent restenosis of post-irradiated carotid stenosis

使用塗藥囊球預防放射線頸動脈狹窄之支架再狹窄

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吳嘉紘

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Background: To investigate the technical safety and outcome of in-stent restenosis (ISR) prevention with drug-eluting balloon (DEB) in patients with postirradiated carotid stenosis (PIRCS) undergoing percutaneous angioplasty and stenting (PTAS).

Methods: From 2017 to 2021, we prospectively recruited patients with severe PIRCS for PTAS. They were randomly separated into two groups based on endovascular techniques performed with and without DEB. Pre- and early postprocedural (within 24 hours) MRI, short-term ultrasonography (6 months after PTAS), and long-term CTA/MRA (12 months after PTAS) were performed. Technical safety was evaluated based on periprocedural neurological complications and recent embolic ischemic lesions (REIL) number in the treated brain territory on diffusion-weighted imaging (DWI) of early postprocedural MRI.

Results: Sixty-six (30 with and 36 without DEB) subjects were enrolled. Technical success was achieved in 65 patients (98.5%). For the 65 patients in the DEB vs. conventional groups, technical neurological symptoms within 1 month (1/29 [3.4%] vs. 0/36; $p = 0.123$) and REIL numbers within 24 hours (1.0 ± 2.1 vs. 1.3 ± 1.5; $p = 0.592$) after PTAS showed no differences. PSV on the short-term ultrasonography was significantly higher in the conventional group (104.13 ± 42.76 vs. 81.95 ± 31.35; $p = 0.023$). The in-stent stenosis degrees (45.93 ± 20.86 vs. 26.58 ± 8.75; $p < 0.001$) were higher, and more subjects (n = 8, 38.9% vs. 1, 3.4%; $p = 0.029$) with significant ISR (≥ 50%) were noted in the conventional groups on the long-term CTA/MRA.

Conclusion: Primary angioplasty with DEB in PTAS of PIRCS can significantly reduce the risk of ISR within 12 months. The technical safety of PTAS was similar with and without DEBs.

Imaging and intervention of intracranial artery stenosis

顱內動脈狹窄的影像診斷與介入治療

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Background: Percutaneous transluminal angioplasty and stenting (PTAS) is of one of the treatment choices in patients with severe intracranial artery stenosis (SICAS) after medical failure. High-resolution vessel wall imaging (HR-VWI) has been widely applied to evaluate the diverse etiologies of SICAS, including atherosclerosis, dissection and vasculitis. This technique was also used in the evaluation of lesion characteristics, including stiffness and treatment response, which provide clues for patient selection before PTAS. Hard stenotic lesions are commonly seen in atherosclerosis and dissection in atherosclerosis, whereas soft stenotic lesions are more likely in dissection. Soft stenotic lesions of SICAS have a better outcome after PTAS than hard stenotic lesions. The purpose of this speech was to demonstrate the early and delayed changes on HR-VWI of patients with SICAS who underwent PTAS and to correlate these changes with patient outcomes at the 1-year follow-up.

Methods: The study included 24 severe intracranial artery stenosis (SICAS) patients undergoing PTAS with Wingspan Stent between 2018 and 2020 and had a 1-year follow-up. Three HR-VWI sessions (preprocedural, early [within 24 hours] and delayed postprocedural [134.7 ± 27.1 days)]) in each subject were performed with 3-Tesla MRI. We evaluated periprocedural HR-VWI changes in patients with and without recurrent cerebral ischemic symptoms (RCIS) within 1-year follow-up.

Results: On CE-T1WI of the patients without RCIS, a significant decrease in enhanced area was observed on early postprocedural (0.04 ± 0.02 cm2, p = 0.001) and delayed postprocedural (0.04 ± 0.02 cm2; p = 0.001) HR-VWI compared to preprocedural (0.07 ± 0.02 cm2) HR-VWI. Patients with RCIS demonstrated no significant loss of enhanced area on CE-T1WI of early postprocedural HR-VWI (p = 0.180). Significant decreases in calibrated T1 signals were observed in both presence (1.77 ± 0.70 vs. 0.79 ± 0.52; p = 0.018) and absence (1.42 ± 0.62 vs. 0.83 ± 0.40; p = 0.001) of RCIS in early postprocedural HR-VWI.

Conclusion: The preliminary results showed the presence of reduced contrast enhancement immediately after PTAS may indicate less recurrent stroke events within 1 year. We also present both imaging diagnosis of the many etiologies of intracranial artery stenosis to enhance the most appropriate management.

Brain arteriovenous malformation: From basic to real world

腦動靜脈畸形：從基礎到現實世界

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Brain arteriovenous malformation (BAVM) is a congenital abnormality in the brain's vascular system that results in the direct connection of arteries and veins, bypassing the capillary bed.Single nucleotide mutation in TNFa and IL-6 have been intentified in BAVM patients, and associated with elevated IL-6 and Vascular endotheial growth factor.BAVMs mostly presented with hemorrhage, seizure; less than 20% BAVM areasymptomatic. Treatment options for AVMs include surgical removal, embolization, and radiosurgery. The choice of treatment depends on the size, location, and angioarchitecture of the AVM, as well as the patient's age and overall health. In recent years, advances in imaging and treatment techniques have improved the prognosis for patients with AVMs. However, further research is needed to fully understand the underlying causes and optimal management of AVMs.

Complications of flow diverter manages intracranial aneurysms

使用分流支架治療顱內動脈瘤

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Flow-diverter (FD) was designed as a single-stent treatment solution for intracranial aneurysms by endoluminal reconstruction instead of endosaccular coiling. Most FD have denser metallic surface coverage (MSC) with smaller porosity than traditional stent, the MSC coverage of FDs varied from 30-35%. FD take advantage of changing the parent artery/aneurysm sac interface altering in-flow and out-flow hemodynamic, to promote aneurysm thrombosis. Subsequent neointimal overgrowth covers the stent reconstructing the parent artery and eliminating the aneurysm/parent vessel interface with maintaining the patency of side branch of parent artery. As opposed to aneurysm coiling, FD causes aneurysm to thrombosis gradually rather than immediately at the end of the procedure. Several systematic reviews and meta-analyses have demonstrated the rate of complete obliteration (CO) of aneurysm varied from 76 to 81.5% depended on the aneurysm size, location and follow-up time frame.

The potential complication rates for aneurysms treated with FD were comparable to traditional coil embolization. The overall complication rate of FD to treat intracranial aneurysm was 17%. The morbidity and mortality of FDS were varied from 3.5%-9.4% and 3.4%-4.1%, respectively. These complications were significantly higher in those aneurysms of ruptured, large/giant or fusiform, wide-neck, distal aneurysms or aneurysms in posterior circulation, particularly in posterior circulation, which may up to 44.7% of patients. The major complication of FD was symptomatic ipsilateral ischemic stroke of in-stent thrombosis of branch vessels occlusion, resulting from poor apposition of FD or insufficient dual anti-platelet treatment (DAPT) because of clopidogrel resistance. Most immediate FD-related ischemic strokes can be solved by balloon angioplasty or catheter/guide massage to improve FD apposition, plus Glycoprotein IIb/IIIa intravascular infusion to lysis the early clots in stent or distal arterial branch. The late complication included in-stent arterial stenosis, which may occur in 20-30% of patient, and most were asymptomatic. Early and late intracranial hemorrhage was uncommon and occurred in less than 20%, however it was devasting because aggravate by DAPT.

The potential procedural complications were low treated by FD with78%-85% CO of aneurysm in a midterm DSA follow-up with, FD was proven to be both effective and safe in most intracranial smaller aneurysms.

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癌症精準治療之最新進展

The Latest Advances in Precision Cancer Treatment

協辦單位：國立陽明交通大學腫瘤惡化卓越研究中心

時　間：112年7月8日　09:00~12:00
Time：July 8, 2023　09:00~12:00

地　點：臺北榮民總醫院 重粒子中心會議室
Place：Heavy Ion Therapy Center, Taipei Veterans General Hospital

癌症精準治療之最新進展

The Latest Advances in Precision Cancer Treatment

CAR-T manufacturing and applications: Recent progress and perspectives

CAR-T 細胞製程與疾病應用之最新進展

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Patients with relapsed or refractory B-cell acute lymphoblastic leukemia have a poor outcome. In 2011, a clinical trial showed durable long-term complete remissions in patients with B-cell malignancies receiving infusions of CD19-specific chimeric antigen receptor (CAR)-T cells. The editors of Science Journal have announced cancer immunotherapy as the year's breakthrough for 2013. In 2015, the first child Emily Whitehead enrolled in a CAR-T clinical trial for patients with B cell malignancies was invited to the White House for President Barack Obama's announcement of the Precision Medicine Initiative. In addition, the Food and Drug Administration (FDA) made history by approving Kymriah, the first living drug, for childhood leukemia treatment on August 30, 2017.

However, CD19-positive or -negative relapses because of poor T-cell persistence or CD19 antigen escapes have occurred in about half of the patients receiving CD19 CAR-T immunotherapy. As we learned from chemotherapy, preventing leukemia relapse requires multiple agents. The same concept may be suitable for immunotherapy. For relapse associated with CD19-negative clone selection or down-regulation, a single CAR construct incorporating CD19/CD20 or CD19/CD22 for dual targeting could be more effective at reducing relapse associated with antigen escape. On the other hand, poor persistence-related relapse can be improved by more stem memory T cells, 41BB incorporation, cytokine signaling, and humanized single-chain variable fragment (scFv). Clinical trials evaluate the next-generation CAR-T to enhance the anti-tumor effect and minimize toxicity.

Another application of CAR-T is CD7 CAR-T treating T-cell malignancies. Importantly, CAR expression in T lymphocytes caused fratricide due to the presence of CD7 in the T cells themselves. Therefore, to downregulate CD7 and control fratricide, a protein expression blocker was used based on an anti-CD7 single-chain variable fragment coupled with an intracellular retention domain. This strategy has demonstrated efficient expansion and achieved a high complete remission rate with a manageable safety profile in clinical trials. Notably, although patients' CD7-positive normal T cells were depleted, CD7-negative T cells expanded and likely alleviated treatment-related T-cell immunodeficiency.

Revolutionizing and beckoning of new era of mRNA cancer therapeutic vaccines and immunotherapy

mRNA 癌症疫苗和免疫治療的新時代

Carlos Linn

林錦洲

Oncology (Immuno-Oncology) Clinical Development, Global Product Development, Pfizer, Inc.

輝瑞大藥廠 全球產品研發 腫瘤 (免疫腫瘤) 臨床開發

The mRNA vaccine technologies were initially introduced from original cancer vaccine research, but expedited large-scale and prompt vaccine development has been achieved on the anti-contagious (SARS-CoV-2) mRNA vaccines. The renaissance of mRNA-based cancer therapeutic vaccines heads on the promising aspirations onward for anti-cancer treatment.

The mRNA-based vaccines exhibit several potential advantages relative to previous trials of conventional vaccination for cancer treatment, namely, they involve neither the need for transfected dendritic cells (DCs) nor the transfection by virus vectors (e.g., adenovirus). The transfection of tumor-associated-neoantigens (TAAs) encoding mRNA in the lipid nanoparticle (LNP) extends the scope from non-specific, on-shelf, and shared TAAs to precise, tumor-tissue-driven, and personalized TAAs for the applications, including cancer vaccines, anti-neoplastic proteins, and T-cell immunotherapy of T cell receptor-engineered-T cells (TCR-T) or chimeric antigen receptor–T cells (CAR-T) implementations.

This presentation will illustrate the essential factors that contribute to the optimization of mRNA cancer vaccine, including the production of effective mRNA transcripts by nucleoside modification and delivery systems, and the applications in manufacturing in brief. These characteristics and advantages of mRNA-based cancer vaccines or immunotherapy improve the bandwidth of anticipated responsiveness to anti-cancer efficacy with possibly lower toxicity. Multiple mRNA vaccine platforms have demonstrated feasibility in treating several types of cancers in humans.

Addressing the portfolio of mRNA vaccines for the potentialities of cancer treatment based on principal interactions of patients' cells producing protein fragments based on a tumor's genetic mutations, prompting the immune system to find other cells with the mutations/TAAs and attack the tumor cells that remain. The basic principle of mRNA therapeutics involves the delivery of in vitro transcribed mRNA into a target cell, where cellular machinery translates the mRNA into a functional protein. The mRNA transcripts are translated directly into the cytoplasm and then the resulting antigens are presented to antigen-presenting cells to stimulate an immune response. Alternatively, dendritic cells can be loaded with either tumor-associated antigens mRNA or total tumor RNA and delivered to the host to elicit specific innate as well as adaptive immunities. Non-viral vector but lipid nanoparticles coating delivery platform used for mRNA vaccines is becoming an attractive platform for cancer immunotherapy.

Next-generation sequencing orientated cancer therapy

次世代基因定序導引下的癌症治療

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Next-generation sequencing (NGS), also known as high-throughput sequencing, is a set of modern technologies that enable researchers to sequence DNA and RNA much faster and more efficiently than traditional sequencing methods. NGS technologies are capable of sequencing millions of DNA fragments in parallel, allowing researchers to analyze entire genomes or transcriptomes in a single experiment.

NGS-orientated cancer therapy is a form of personalized medicine that uses genomic sequencing technologies to analyze a patient's tumor and tailor their cancer treatment to their specific genetic profiles. It is a promising approach that enables oncologists to identify the specific mutations driving the cancer, predict how it will behave, and select the most effective treatment options with fewer side effects possibly.

In this talk, the revolution of clinical study design, clinical application of NGS-orientated cancer therapy, and the operation status of molecular tumor board in Taipei Veterans General hospital will be introduced.

Antibody-drug conjugate: New weapon of cancer treatment

抗體藥物複合體：抗癌新治療武器

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Antibody-drug conjugates (ADCs) have emerged as a promising class of therapeutics for the treatment of cancer. ADCs are a type of targeted therapy that combines the specificity of monoclonal antibodies with the potency of cytotoxic drugs. The concept behind ADCs is to selectively deliver a cytotoxic drug to cancer cells while sparing normal tissues, thereby minimizing systemic toxicity and maximizing therapeutic benefit.

ADCs consist of three components: an antibody that targets a specific antigen expressed on cancer cells, a cytotoxic drug that kills the cancer cells, and a linker that connects the two components. The linker is designed to be stable in the bloodstream but to release the cytotoxic drug once the ADC is internalized by the cancer cell.

Several ADCs have been approved for the treatment of cancer, including brentuximab vedotin and ado-trastuzumab emtansine. These ADCs have shown efficacy in the treatment of Hodgkin lymphoma, non-Hodgkin lymphoma, and breast cancer, among others.

Despite the success of these ADCs, there are still challenges that need to be addressed, such as improving the design and stability of the linker, increasing the potency of the cytotoxic drug, and identifying new tumor antigens that can be targeted by ADCs.

Overall, ADCs represent a promising new weapon in the fight against cancer, and ongoing research in this field is expected to lead to the development of even more effective therapies in the future.

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臺北榮總重離子治療展望

Carbon Ion Therapy's Future Prospects at Taipei Veterans General Hospital

時 間：112年7月8日 13:30~17:30

Time：July 8, 2023 13:30~17:30

地 點：臺北榮民總醫院 重粒子中心會議室

Place：Heavy Ion Therapy Center,
Taipei Veterans General Hospital

臺北榮總重離子治療展望

Carbon Ion Therapy's Future Prospects at Taipei Veterans General Hospital

Heavy ion therapy for prostate cancer in Osaka HIMAK

大阪 HIMAK 碳離子治療前列腺癌臨床經驗

Osamu Suzuki

Department Radiology, Osaka Heavy Ion Therapy Center, Osaka, Japan

In the four years since the start of treatment in October 2018, we have treated 2400 patients at Osaka Heavy Ion Therapy Center. The breakdown is 70% for prostate cancer, followed by 9% for liver, head and neck, and pancreas.

Prostate cancer accounts for the largest number of heavy ion radiotherapy patients in Japan, and our center treats approximately 400 patients annually.

At the Osaka Heavy Ion Therapy Center, we are working on IGRT by placing a gold marker in the prostate, and we are trying to reduce the risk of the prostate detaching from the PTV by aligning the position with the gold marker after bone matching. One aspect not found in conventional X-ray treatment planning is that the irradiation plan must be made over a wider range than the conventional bone matching method in order to ensure changes in the dose distribution due to relative movement of the target volume.

A multicenter analysis by the JCROS Group in Japan reported that the 5-year PSA control rate was 92/89/92% in the low-, intermediate-, and high-risk groups, respectively. Long-term results from QST hospitals using the current standard dose of 51.6 Gy(RBE)/12fr were 89/90/88% at 5 years and 89/80/79% at 7 years. showed a slight downward trend over the long term. In both cases, the incidence of toxicity is low, with late toxicity of G2 or higher being 6% in the urinary tract and less than 1% in the gastrointestinal tract.

In addition, long-term results of heavy ion radiotherapy alone in the low-risk group were also reported from QST hospital, with a 10-year PSA control rate of 73% and a local non-recurrence rate of 87%. The survival rate is good, but it is necessary to consider whether it is recommended as a treatment option for young, low-risk patients.

The number of cases of liver cancer and pancreatic cancer is also increasing, and expectations for heavy ion radiotherapy are high, and prospective data accumulation is desired.

Carbon ion radiation therapy in the management of sarcoma

碳離子放射治療在惡性肉瘤的應用

Cheng-Ying Shiau

蕭正英

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Carbon Ion Radiation Therapy (CIRT) and proton therapy are both charged particle therapy featuring Bragg peak phenomenon, which has the advantages of reduced integral dose compared to photon therapy. Compared to proton therapy, the Bragg peak of CIT has a sharper lateral dose distribution, even though there is some negligible fragmented tail.

Radiobiologically, CIRT is better than proton therapy with the two following facts: 1) CIRT's radiobiological effectiveness (RBE=2~3) is higher than proton (RBE=~1.1), and 2) CIRT's oxygen enhancement ratio (OER=1.5~1.7) is lower than proton (OER=2.3~2.6). With high RBE, CIRT is theoretically better than proton therapy in the management of radioresistant tumors, such as chordoma and chondroscarcoma. With low OER, CIRT is potentially superior to proton therapy in the treatment of tumors with large hypoxic fraction.

The radiation dose of CIRT is clinically reported as Gy RBE, which is physical dose adjusted by RBE. The RBE of CIRT is not a static single value and depends on the actual average Linear Energy Transfer (LET) of the spread-out Bragg peak (SOPB).

There are challenges with CIRT, however. The high RBE of CIRT is a double-edged sword that even CIRT is highly effective against malignant tumor, it may also incur significant normal tissue damage. This is the reason why most CIRT protocols deal with GTV only and CIRT could serve as an ultimate form of radiosurgery. The therapeutic ratio of CIRT in the management of subclinical disease is not well studied. Combined photon and carbon therapy could expand the indications of CIRT.

Taipei Veterans General Hospital started the commissioning clinical trial of carbon ion therapy (CIRT) on 2022/6/30, and has just completed the trial of 6 patients, including two prostate cancers, one sacral chordoma, one hepatocellular carcinoma, one lung cancer and one parotid gland cancer, to verify the safety of the advanced radiation therapy. The CIRT of the 6th patient was completed on 2022/9/30.

The chordoma patient received 64 Gy^{RBE} in 16 fractions from 2022/7/26 through 2022/8/23. Even though the sacral chordoma is very large, 12 cm in maximum diameter, the CIRT course was smooth and the toxicity was minimum. The radiation dermatitis was only grade 2, which is very mild for the relatively superficial tumor extension. Sigmoidoscope at one week after CIRT showed no sign of radiation dermatitis, which confirmed the well execution of CIRT plan in prone position with daily IGRT and anal tube to remove rectosigmoidal gas. During the CIRT course, weekly adaptive CT were performed. Mild transient swelling of the tumor without the need of re-planning was found.

The outcome of sarcoma treated by CIRT in the literature will be reviewed along with presentation of the chordoma cases treated at Heavy Ions Therapy Center (HITC), Taipei VGH.

The roles of carbon ion therapy in the era of combinational anticancer therapy

碳離子療法在聯合抗癌治療時代的角色

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Carbon ion radiotherapy is an emerging cancer treatment that deliver high doses of radiation to tumors while causing minimal harm to surrounding healthy tissue. This technology has demonstrated tremendous promise for the treatment of various types of cancer, including sarcoma, prostate, liver, pancreatic, and lung cancer etc.. In recent years, novel systemic treatments, such as immunotherapy and targeted therapy, have been developed and have demonstrated promise for enhancing patient outcomes. Combining carbon with these novel systemic treatments has the potential to further increase the efficacy of cancer treatment by targeting the tumor from numerous angles. Immunotherapy, for instance, can stimulate the patient's immune system to recognize and attack cancer cells, whereas carbon or heavy ion radiotherapy can destroy cancer cells directly through radiation. Targeted therapy can precisely target cancer cells with molecular abnormalities, whereas radiotherapy with carbon or heavy ions can target the tumor itself. In addition, the combination of these therapies may enhance the efficacy of radiation therapy by sensitizing cancer cells to its effects. Ongoing studies are investigating the potential benefits and optimal combination strategies of these cancer treatments. Combining carbon or heavy ion with novel systemic therapies has the potential to revolutionize cancer treatment and substantially improve patient outcomes in the future.

Clinical results and future perspectives of carbon ion radiotherapy for pancreatic cancer

碳離子治療胰腺癌的臨床結果和未來展望

Makoto Shinoto

QST Hospital, National Institutes for Quantum Science and Technology, Chiba, Japan

In Japan, pancreatic cancer is as the fourth most common cancer-related cause of death. The survival rates for this lethal cancer remain in the single digits, making effective therapy a constant challenge. Although the only opportunity for a cure is through radical resection, over half of the patients already have metastases at the time of diagnosis. In close to one-third of cases, vascular invasion causes unresectable locally advanced pancreatic cancer (LAPC) diagnosis. Advanced pancreatic cancer patients have had better results when treated with multi-agent chemotherapy regimens such as leucovorin, fluorouracil, irinotecan, and oxaliplatin (FOFLFIRINOX) and gemcitabine with nab-paclitaxel (GnP). The use of radiation is controversial on the other hand. Recent reports indicate that the conventional dose of radiotherapy may not be effective with no overall survival improvement of chemoradiotherapy compared with chemotherapy alone.

Carbon-ion radiotherapy was the first in the world to safely succeed in dose escalation to LAPC and has achieved favorable results in treating LAPC. The local control rate improved with higher doses, which may have helped to further enhance the survival outcome. Current dose intensities, meanwhile, are still insufficient to manage LAPC and achieve long-term survival. Therefore, to overcome this dreadful pancreatic cancer, we are carrying out further dose-escalation research.

Carbon-ion radiotherapy indications and clinical trial results at Taipei Veterans General Hospital

臺北榮總重粒子治療適應症及臨床試驗成果

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Carbon-ion radiotherapy (RT) is a revolutionary radiation technology with several physical and biological benefits. Because of the physical properties of the "Bragg Peak," carbon-ion RT may reduce doses to normal tissue and reduce the risk of second cancer in patients. Carbon-ion RT has shown higher efficacy against aggressive and radioresistant tumors in hypoxic microenvironments. Carbon-ion RT is also appropriate for hypofractionation treatment, and laboratory studies have shown that it can increase immunogenicity and reduce cancer cell invasion and metastasis.

Carbon-ion RT has the potential to treat a variety of solid tumors. We are currently concentrating on imaging visible tumors on inoperable patients or patients who have declined surgery. Carbon-ion RT is effective and safe for patients with head and neck cancer, lung cancer, liver cancer, pancreatic cancer, prostate cancer, recurrent colon and rectal cancer, sarcoma, or chordoma, according to past clinical evidence. It may also be used to treat renal cell carcinoma, gynecological cancer, esophageal cancer, ophthalmic cancer, recurrent lymphadenopathy, and oligometastatic cancer. Other cancer indicators are being researched.

Between June and September 2022, the carbon-ion facility at Taipei Veterans General Hospital successfully treated six cancer patients, including two prostate cancer patients, one chordoma patient, one liver cancer patient, one lung cancer patient, and one head and neck cancer patient. Follow-up investigations demonstrated that carbon-ion RT is a safe and effective therapy for inoperable patients. The heavy ion facility at Taipei Veterans General Hospital is scheduled to open in May 2023. We anticipate that carbon-ion RT will play a significant role in the treatment of solid tumors in Taiwan in the future.

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直腸癌治療新趨勢

Emerging Trends in Rectal Cancer Treatment

時　間：112年7月8日　　13:30~17:30

Time：July 8, 2023　　13:30~17:30

地　點：臺北榮民總醫院 致德樓第三會議室

Place：The Third Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

直腸癌治療新趨勢
Emerging Trends in Rectal Cancer Treatment

The experience of colorectal lung metastasectomy in Taipei Veterans General Hospital

分享臺北榮民總醫院對結直腸肺轉移切除的經驗

Hao-Wei Teng

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Colorectal cancer (CRC) is a prevalent cancer worldwide. In Taiwan, it is the third leading cause of cancer-related deaths as of 2017. Around 40% of CRC patients progress to metastatic CRC (mCRC), with the liver being the most common site of metastasis and the lungs being the secondary site.

Despite advances in systemic treatments, the curative intent treatment for patients with oligometastasis remains metastasectomy, which involves the surgical removal of the metastatic lesions. Combining colectomy with metastasectomy provides a curative opportunity, with a 5-year disease-free survival rate ranging from 20% to 25% in patients who undergo colorectal metastasectomy.

Today, we will be sharing the experience of Taipei Veterans General Hospital in treating colorectal lung metastasis. Generally, colorectal lung metastasectomy is recommended by chest surgeons when oligo lung metastasis is present. However, the optimal timing for colorectal lung metastasis surgery remains uncertain. Our objectives are as follows:

To report the natural history of colorectal lung metastasis.

To compare the outcomes between sequential and selective lung metastasectomy.

Choices of radiotherapy for rectal cancer

直腸癌放射治療的選擇

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Neoadjuvant radiotherapy (RT) with or without chemotherapy followed by total mesorectal excision and adjuvant chemotherapy is the current standard of care for locally-advanced rectal cancer. Traditionally, both neoadjuvant long-course chemoradiotherapy (CRT) (45-54 Gy in 25-28 fractions) and short-course RT alone (25 Gy in 5 fractions) are the mainstream protocols for neoadjuvant protocols. The most commonly used concurrent chemotherapy regimens along with long-course RT are capecitabine or infusional 5-FU. However, in our hospital, we have the experience of using long-course RT combined with mitomycin-C (MMC) and oral tegafur-uracil (UFUR) as neoadjuvant treatment for more than 10 years. In a retrospective review of our patients, using this combination contributed to pathological complete response (pCR) rate 22.1%, down-staging rate 73.3%, and the 5-year overall survival was around 80%. In this study, we also found that compared to RT+UFUR without MMC, adding MMC might increase the down-staging and improve overall survival. Besides, pre-CRT CEA carcinoembryonic antigen (CEA) level and the change of CEA level after CRT have predictive value on pCR rate and disease-free survival.

Recently, increased evidences have shown that total neoadjuvant therapy (TNT) might increase the patient's compliance with chemotherapy compared to adjuvant chemotherapy. Besides, TNT strategy might result in a better pCR rate and disease control compared to neoadjuvant long course RT followed by adjuvant chemotherapy. Therefore, TNT gradually becomes the standard of care as a neoadjuvant treatment.

Regarding non-operative approach after CRT, some retrospective literatures revealed that watch and wait for patients with clinical CR after neoadjuvant treatment results in a 2 -year local-regional regrowth rate of 15-35% though most of the regrowth is salvageable. We need more well-designed randomized trials to confirm the efficacy and safety of organ preservation strategies for rectal cancer.

Carbon-ion radiotherapy for locally recurrent rectal cancer: Experience from Japan

重粒子在直腸癌局部復發的日本經驗分享

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It is difficult to achieve a cure in patients with unresectable locally recurrent colorectal cancers (LRCRC) using conventional chemotherapy or chemoradiotherapy. Furthermore, treatment options will differ depending on the patient's prior experience with radiation therapy. Photon re-irradiation to the local recurrent tumor is often challenging due to dose constraints on normal organs. In Japan, Carbon-ion radiotherapy (CIRT) has been experimentally started since 1994, and clinical applications have been advancing since 2003. Based on the experience, we are convinced that it can be curative for both radiotherapy-naive (nRT) and re-irradiation (reRT) patients.

CIRT was administered daily on 4 days/week for 16 fractions. The total irradiated dose was set at 73.6 Gy (relative biological effectiveness–weighted dose [RBE]) for nRT cases and 70.4 Gy (RBE) for reRT patients. An immobilization device was prepared for each patient. Histological examination was optional, but the clinical diagnosis was based on CT, MRI, and PET scans.

More than 600 cases were treated at the NIRS–QST hospital between 2003 and 2019. We selected 390 nRT cases and 83 reRT cases with no synchronous distant metastases at the beginning of CIRT. The median follow–up period from the initiation of CIRT was 48 (5–208) months. The 5–year OS rates were 50% (45–55%) and 50% (38–61%), respectively (p = 0.55). The 5–year LC rates were 72% (67–78%) and 69% (55–81%), respectively (p = 0.56). Grade 3 or more severe late toxicities were observed in 5.9% of nRT cases, while these were observed in 26·5% of reRT cases.

Our results suggest that CIRT for LRCRC is an effective and promising treatment for both nRT and reRT cases. It's excellent news that this treatment is now accessible in Taiwan, R.O.C., and that colorectal physicians have innovative alternatives to photon therapy.

The role of transanal mesorectal excision (TaTME) in rectal cancer surgery

經肛門直腸繫膜切除 (TaTME) 於直腸癌手術之角色

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Performing rectal surgery, particularly for lesions located in the mid to lower rectum, presents significant challenges. The difficulties can be amplified in patients who possess a narrow pelvis, obesity, have a large uterus, have undergone radiation therapy, or require re-operative procedures. Transanal total mesorectal excision (TaTME), however, offers an innovative solution since 2010. This transanal approach allows surgeons to direct visualization to the rectum's deepest part, ensuring the safe securing of the distal margin and the ability to perform anastomosis with a single stapling technique.

However, TaTME possesses a distinct and notably steeper learning curve. It integrates a single port technique, necessitates the adept application of good purse-string sutures for complete rectal closure, and requires navigation through an anatomy that is altered compared to the transabdominal view. While retrospective studies offer encouraging indications for TaTME, it's crucial to recognize that the long-term oncological outcomes are still pending validation from ongoing clinical trials.

The application of da Vinci robotic system in rectal cancer surgery

達文西機械手臂於直腸癌手術之應用

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The da Vinci robotic system is a minimally-invasive surgical instrument composed of an ergonomic surgeon console, high-resolution 3D vision system, and four robotic arms. The robotic system is increasingly being used in rectal cancer surgery.

Using the da Vinci robotic system for rectal cancer surgery has a number of benefits. The 3D vision system provides the surgeon with a high resolution, magnified view of the surgical field, allowing them to accurately identify and remove tumors. The robotic arms give surgeons greater dexterity and control than traditional laparoscopic surgery, resulting in less tissue damage and pain. The minimally-invasive approach also leads to less blood loss and shorter hospital stays. Finally, the da Vinci system allows surgeons to perform surgical tasks with accuracy and precision, increasing the success rates of rectal cancer surgeries.

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精準醫療與高階影像在健康管理的運用

Precision Medicine and Advanced Image in Healthcare

時 間：112年7月8日 13:30-17:10

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Place：The Fourth Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

精準醫療與高階影像在健康管理的運用

Precision Medicine and Advanced Image in Healthcare

Big data analysis and application in health check

健檢大數據資料之分析與運用

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Big data refers to extremely large and complex datasets that cannot be easily analyzed or processed using traditional data processing tools or methods. Big data is characterized by its volume, velocity, and variety, meaning that it includes large amounts of data from multiple sources, is generated at high speeds, and comes in a variety of formats and types. Big data could be transformed into smart data using advanced analytics and data processing techniques (e.g. data preprocessing, data integration, AI-powered analysis, humanizing data visualization, and real-time analytics) to extract meaningful insights and make data more actionable.

Smart data can be used in health check-ups to improve the accuracy and effectiveness of the tests, as well as to provide patients with personalized recommendations for maintaining their health. Personalized health assessments take into account medical history, lifestyle, and risk factors by integrating a variety of electronic health records. Of note, continuous monitoring by wearable device provides invaluable real-time information along with traditional medical examinations. These patient-generated health data is burgeoning over recent years, and could be generated via wearables, mobile apps, and other digital health tools. By collecting and analyzing smart data, healthcare providers can gain a more comprehensive understanding of a patient's health status, behaviors, and needs; improve patient outcomes; optimize clinical processes; and reduce costs, thereby realizing smart health. Another way to use smart data in health management is through predictive analytics. Predictive analytics uses machine learning algorithms and other data analysis techniques to identify patterns and predict future outcomes based on historical data. Healthcare providers can use predictive analytics to identify patients at risk for certain health conditions or complications and intervene early to prevent adverse outcomes.

While advancing health check from big data and digital health to smart data and smart health, we improve the accuracy and efficiency of healthcare delivery, promoting early intervention and disease prevention, thus facilitating targeted interventions and programs to improve health outcomes.

Quality improvement of endoscopy in health check

健檢胃腸鏡檢查之品質提升

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Use of mucolytic agent (pronase) and anti-foaming agent (simethicone) can improve mucosal visibility during upper GI endoscopy. CO2 (versus air) insufflation and simethicone significantly reduces abdominal pain during and following the colonoscopy. Commercial low residual diet improves the quality of colon preparation and compliance of subjects.

The risk of post-colonoscopy colorectal cancer is related to the adenoma detection rate (ADR) of the endoscopist, the cecum intubation rate (CIR) and the degree of bowel cleansing of the subject. Each 1% increase in the adenoma detection rate associated with a 3% decrease in the risk of CRC. However, adenomas can be neglected during screening, with reported missing rates of up to 25% due to both adenoma and operator.

Optimal maneuvering of the colonoscope to expose mucosa behind folds, adequate distension, clean colon, and sufficient inspection time to visually process the exposed mucosa. Electronic chromoendoscopy, mucosal exposure devices such as Endocuff, ultra-wide angle endoscopes, water exchange, second exam of right colon, and adequate withdrawal time improve adenoma detection rate.

Regarding bowel preparation, split-dose bowel preparations provided excellent or good colon cleansing more frequently than day-before bowel preparation, The second dose should be administered between 3–8 hours before the planned start of the colonoscopy procedure. Split-dose SPMC and PEG have similar results for adequacy of bowel preparation. Split-dose SPMC associated with increased patient tolerability, compliance (adherence rates), and less side-effects (blood e-, nausea, abdominal pain or bloating)

Meta-analysis analysis showed that artificial intelligence (AI)-based polyp detection systems during colonoscopy increased lesion detection and improved colonoscopy quality. A multicenter randomized controlled trial showed AI-assisted colonoscopy improved overall ADR, advanced ADR, both in the expert and nonexpert attending endoscopists.

Whole genome sequencing and precision medicine in health check

全基因檢測與健康醫學在健康受檢者之角色

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With the successful decoding of the human genome and the rapid advancements in next-generation sequencing technology, whole genome sequencing (WGS) has emerged as an increasingly accessible and cost-effective method for examining the entire genetic makeup of an individual. This powerful tool not only enhances the precision of medication treatments but also enables the identification of individuals at elevated risk of developing diseases even before the manifestation of any symptoms.

As we move towards an era of preventive medicine, the information obtained through WGS is expected to significantly enhance our comprehension of the state of our bodies, providing us with the opportunity to proactively manage our health risks based on the results of these tests. However, the processing and analysis of the massive amounts of data generated by WGS have emerged as a critical challenge that must be addressed to fully leverage the potential benefits of this technology.

To address this problem, our center has collaborated with a bioinformatics service company to develop a "rapid real-time WES/WGS analysis system" by combining gene analysis technology, cloud computing, big data, and artificial intelligence technology. The system boasts a user-friendly interface and a comprehensive range of analytical capabilities, including pharmacogenomics analysis, constitutional analysis, proactive analysis, and HLA typing analysis.

Moreover, the system incorporates a genomic AI analysis system (strata finder) for risk assessment of complex diseases such as asthma, AMI, and stroke with an accuracy of 99% or higher. With the aim of promoting precision medicine in Taiwan, our system represents a critical step towards the realization of the "prevention is better than treatment" paradigm in public healthcare.

The role of coronary computed tomography angiography in the primary management of coronary atherosclerosis

心臟冠狀動脈造影在心血管疾病之診斷與運用

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Coronary artery disease (CAD) remains one of the leading causes of mortality and morbidity in Taiwan. In the past decades, coronary computed tomography angiography (CCTA) has become a powerful tool in the evaluation and management of CAD. The diagnostic and prognostic value of CCTA has been extensively demonstrated in both large observational studies and clinical trials among stable chest pain patients. The quantification of coronary artery calcium score (CACS) is a well-established predictor of cardiovascular morbidity and mortality in asymptomatic subjects. Besides CACS,

the main strength of CCTA is the accurate assessment of the individual total atherosclerotic plaque burden, which holds important prognostic information. In addition, CCTA, by providing detailed information on coronary plaque morphology and composition with identification of specific high-risk plaque features, may further improve the risk stratification beyond the assessment of coronary stenosis, even by invasive coronary angiography. In this speech, starting from the role of CACS and moving beyond coronary stenosis, I would like to evaluate the existing evidence of the prognostic effectiveness of the CCTA strategy in real-world clinical practice, focusing mainly in individuals receiving health check-up as well as patients with stable angina.

Whole body-MRI in precision health

全身磁振造影應用於精準健康

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Precision health focuses on maintaining health of general population rather than treating disease of individual patient. With broader implementation of magnetic resonance imaging (MRI) in precision health, imaging becomes one of crucial parts of health screening. MRI provides high spatial resolution and superior tissue contrast images with no ionizing radiation, which is a safe and powerful tool of imaging screening for general population. Whole-body MRI (WB-MRI) usually covers from vertex to upper thigh and can provide morphological and functional information in an acceptable scan time enabled due to advances of imaging technology.

There are increasing clinical use and research of WB-MRI since the late 1990s. Applications of WB-MRI include cancer staging in oncology, cancer screening in population with cancer predisposition syndromes, musculoskeletal conditions, pediatrics, rheumatology and screening in general population. During the past two decades, the research and reviews of WB-MRI in screening of healthy individuals focus on imaging techniques, diagnostic yields, and clinical polices for further management. In Taiwan, WB-MRI has been implemented in health check in the early 2000s. WB-MRI for screening has inherent limitation in early detection of majority of prevalent or impactful diseases, such as specific cancers (precancerous or early stage of lung, colon, gastric, esophageal, thyroid, and cervical cancers, urothelial carcinoma, skin cancer or leukemia), coronary artery disease, diabetes, metabolic syndrome, dementia and osteoporosis. In addition to WB-MRI, complimentary examinations and multidisciplinary expertise are inevitable for precise and comprehensive healthcare.

Precision health aims for detection of traits or abnormalities that predict the risk of developing diseases, and early detection and targeted interventions to modify the risk. To achieve the goal, collection and analysis of millions of data including genomes, phenomes and exposomes are needed for comprehensive understanding of individual's health status and adoption of actionable strategy. Imaging data from MRI, computed tomography, ultrasound and X-ray is one part of the phenomes.

Emerging trend of WB-MRI in precision health is precision imaging. Combination with complementary tools and cross-field collaboration with biotechnology, bioinformatics, information technology, including analytics and artificial intelligence, are keys to engage in this field.

Low dose chest CT is effective in detecting early lung cancer

低劑量電腦斷層是早期肺癌診斷的利器

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Lung cancer is the leading cause of cancer death in Taiwan. Due to the close relation between clinical staging and prognosis, early stage cancer detection significantly decreases cancer related mortality and improves survival. The randomized controlled National Lung Cancer Screening Trial (NLST, N=53, 454) and Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON, N = 15 792) showcased that in comparison with chest X-ray or no screening, low dose computed tomography (LDCT) reduced the mortality rate of lung cancer in the smoking and aging related high risk groups by 20% and 24% respectively. Since then, LDCT has been accepted as the standard screening imaging modality for lung cancer.

The principle of LDCT is to minimize radiation dose by decreasing the tube current and voltage, applying dose modulation techniques for scanning and iterative reconstruction for image reconstruction while maintaining diagnostic quality.

Literature review covering the potential candidates for LDCT screening, management of screening findings and follow up protocols in addition to the role of artificial intelligence in the reading and workflow for optimal benefit and efficacy will be reviewed. The current status of national LDCT screening in Taiwan will also be addressed.

Lastly, the safety drawbacks and potential concerns of LDCT screening such as the risk of radiation induced cancer, overdiagnosis and overtreatment after detection of nodules along with psychological impact should be taken into consideration. Nevertheless, with evidence from world-wide trials, LDCT remains the best tool for lung cancer detection in high-risk groups.

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全身性紅斑性狼瘡與狼瘡性腎炎近年新進展

Recent Advances in the Management of Systemic Lupus Erythematosus

時 間：112年7月8日 13:30~17:30

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Place：The Fifth Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

全身性紅斑性狼瘡與狼瘡性腎炎近年新進展

Recent Advances in the Management of Systemic Lupus Erythematosus

An overview of systemic lupus erythematosus and lupus nephritis

關於紅斑性狼瘡與狼瘡型腎炎的疾病介紹經驗

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Systemic lupus erythematosus (SLE) is an autoimmune disease that can involve the kidneys, known as lupus nephritis (LN). LN significantly contributes to the mortality and morbidity associated with SLE. Patients with LN have higher standardized mortality ratios and experience severe impairment in health-related quality of life, affecting various aspects of their daily lives.

There are notable ethnicity-related disparities in the prevalence and prognosis of LN. Certain populations, such as African Americans, African Caribbeans, Hispanics, and South and East Asians, have a higher incidence of LN compared to white populations. Genetic factors, including specific risk genes, contribute to the susceptibility to SLE and LN among these ethnic groups. Additionally, socioeconomic determinants of health, such as income, education, access to medical care, and treatment adherence, play a significant role in shaping the prognosis of LN, particularly among underserved populations.

CD8+ effector memory T cells are associated with lupus nephritis, as identified through machine learning analysis of immune cell signatures in juvenile-onset systemic lupus erythematosus. These findings enhance our understanding of the disease's immunological aspects and suggest potential for personalized treatment strategies.

Despite advancements in understanding the pathogenic mechanisms of LN and the availability of treatment options, renal survival rates for LN have reached a plateau or even declined in developed countries. Within a decade of diagnosis, a significant percentage of LN patients progress to end-stage kidney disease. This highlights the urgent need for improved therapeutic strategies that strike a balance between efficacy and toxicity. My talk provides an overview of conventional therapies, recent drug developments, and the potential of precision medicine in managing LN, with a particular focus on targeting type I interferon (IFN) signaling, which has shown promise in clinical trials.

The current treatment options for systemic lupus erythematosus and lupus nephritis

紅斑性狼瘡與狼瘡型腎炎目前的治療選項

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Systemic lupus erythematosus is a systemic autoimmune disease that commonly affects women of childbearing age. Early diagnosis and treatment pose significant challenges for rheumatologists due to the complex and diverse clinical manifestations. In recent years, advancements in medicine have improved the 10-year survival rate of SLE to over 90%. However, the prognosis of this disease is still heavily influenced by lupus nephritis. This speech will focus on the treatment guidelines, with the main emphasis on the real-world data from the Department of Immunology and Rheumatology at Taichung Veterans General Hospital.

The most widely recognized treatment guidelines for SLE are currently those released by the European Union of Rheumatology (EULAR) in 2019. It is worth noting that an updated version is expected to be released in 2023. The Asia-Pacific Association of Rheumatology (APLAR) is set to release its own treatment guidelines for SLE in 2021. Given the high incidence of SLE in Asian countries, this version will incorporate an oriental perspective and comprehensive research based on the Asian population. As a result, it will provide valuable insights as a reference. The American College of Rheumatology (ACR) and the Organization for Improving Kidney Outcomes Globally (KDIGO) have independently published treatment guidelines for lupus nephritis. These guidelines classify lupus nephritis into six categories based on the international classification system, considering the varying prognosis and drug response. Corresponding treatment recommendations are provided within the guidelines.

Based on the past 10 years of treatment experience at Taichung Veterans General Hospital, it has been found that compound drugs primarily based on MPA (mycophenolic acid) yield the best therapeutic results for SLE. Statistically significant associations have been observed between certain active indicators, chronic indicators in pathological sections, chronic nephritis, and mortality. These findings have been published in international journals.

In recent years, biological agents have garnered significant attention as a potential treatment option. Monoclonal antibody targeting BLyS or Interferon have received regulatory approval from the Ministry of Health and Welfare. Starting from October 2022, BLyS-specific inhibitors will be conditionally covered by health insurance, providing a new generation of treatment options for patients with lupus nephritis.

Patient support and self-care of systemic lupus erythematosus and lupus nephritis patients

紅斑性狼瘡及狼瘡性腎炎病人的支持系統與自我照護

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Systemic lupus erythematosus (SLE) is an autoimmune disease. The immune system attacks its own cells and tissues, leading to inflammation and organ damage. The symptoms of lupus vary from person to person, and some symptoms may appear suddenly or develop slowly. They can range from mild to severe, be temporary or persistent. Common symptoms include fever, hair loss, headaches, memory loss, loss of appetite, weight loss, excessive fatigue, skin rashes like a butterfly and discoid rash, weight loss, kidney involvement, photosensitivity, joint pain, and stiffness. It primarily affects females before menopause between the ages of 15 and 45. While each patient's symptoms may differ, the disease activity can fluctuate and generally falls into three patterns: "chronic quiescent," "chronic active," and "relapsing-remitting." The higher the disease activity, the higher the mortality rate for patients.

Organ damage is often irreversible, and over 40% of diagnosed patients experience varying degrees of organ damage within five years. Prolonged disease activity and long-term use of corticosteroids increase the extent of organ damage, making complete remission the primary treatment goal for lupus. Among all complications, renal involvement, known as lupus nephritis, is particularly concerning for doctors and patients, especially in Asians and African Americans who are at a high-risk group for lupus nephritis. About 40% of patients develop lupus nephritis, and 20% may progress to end-stage kidney disease within ten years. Symptoms of lupus nephritis include foamy urine, hematuria, high blood pressure, frequent urination, and unexplained swelling in the legs.

Early detection and treatment are crucial to quickly alleviate active disease, prevent organ damage, and reduce treatment-related toxicity, which are the treatment goals for lupus. Self-care measures include 1. Regular follow-up appointments, 2. Sun protection, 3. Regular exercise, 4. Smoking cessation, 5. Healthy diet, and 6. Early notification to the doctor about pregnancy plans for medication adjustment.

Medications for treatment include corticosteroids, with dosage varying based on disease severity. Despite having many side effects, corticosteroids remain the first-line treatment due to their effectiveness and rapid action. Hydroxychloroquine (Plaquenil) can also stabilize the activity of lupus, especially in patients with antiphospholipid syndrome. It is particularly important to take hydroxychloroquine during pregnancy to stabilize the condition and prevent miscarriage or severe thrombosis. Other important immunosuppressive drugs for the treatment of lupus nephritis include Azathioprine, Mycophenolate mofetil (Cellcept, Myfortic), and Cyclosporine. If control is inadequate, drugs such as Cyclophosphamide or Rituximab may be considered. In addition, a recently approved biologic agent called Belimumab (Benlysta) has been approved by the health insurance system and is effective in treating lupus nephritis as well as other organ system manifestations.

An introduction to comorbidities of systemic lupus erythematosus

系統性紅斑性狼瘡常見的共病簡介

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Lupus, classified as a multifaceted autoimmune disorder, presents numerous potential complications and what are referred to as comorbidities. Comorbidity, a medical term denoting the coexistence of multiple medical conditions within an individual, is frequently observed in lupus patients. On the other hand, a complication refers to a health issue that arises as a consequence of the underlying disease.

Lupus shares a common characteristic with numerous other ailments, whereby it tends to intersect with various health-related concerns. Individuals affected by lupus commonly experience complications and comorbidities such as cardiovascular disease, metabolic syndrome, infections, fibromyalgia, cancer, osteoporosis, depression and anxiety, antiphospholipid antibody syndrome, and other autoimmune diseases

Antiphospholipid Antibody Syndrome (APS) and Lupus Individuals diagnosed with lupus have a significantly heightened risk of developing a condition known as APS. In APS, the body generates antibodies that target the proteins responsible for regulating blood clotting. As a result, individuals with APS tend to experience the formation of blood clots within their arteries and veins, recurrent miscarriages, or thrombocytopenia.

Osteoporosis and Lupus, along with the administration of corticosteroids used to manage lupus symptoms, contributes to the onset of a condition known as osteoporosis, characterized by weakened bones. Both the underlying disease process and the use of steroids in lupus treatment contribute to the deterioration of bone strength and density.

Cardiovascular disease is the leading cause of death in people with lupus. Cardiovascular means heart (cardio) and blood vessels (vascular). Fifty percent experience high blood pressure, and chest pain, atherosclerosis (hardening of the arteries), pericarditis (inflammation of the heart), angina, Raynaud's phenomenon, and other heart and blood vessel issues are common.

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血液製品於與免疫細胞療法的應用

Cell Products Applications for Future Cell Therapy

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Taipei Veterans General Hospital

血液製品於與免疫細胞療法的應用

Cell Products Applications for Future Cell Therapy

The evolution of therapy strategies and optimal use of Blinatumomab in ALL

急性淋巴性白血病治療策略新進展及 Blinatumomab 最佳的治療角色

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Acute lymphoblastic leukemia (ALL) is a type of blood cancer that affects the white blood cells called lymphocytes. Treatment for ALL usually involves chemotherapy, radiation therapy, and stem cell transplantation. However, in recent years, new treatments like immunotherapy have emerged. Blinatumomab is a type of immunotherapy that works by engaging the body's immune system to attack cancer cells. It is used to treat the B-cell precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% and relapsed or refractory B-cell precursor acute lymphoblastic leukemia.

Recent years have witnessed major advances that have improved outcome of adults with ALL. The standard of care could be changing for adults with newly diagnosed Ph– ALL who achieve MRD negativity after induction chemotherapy. In the phase III E1910 trial, an overall survival benefit was derived with the addition of blinatumomab to consolidation chemotherapy, suggesting that even this lower-risk subset of patients may benefit from this bispecific antibody.

Traditionally, Ph+ ALL responds poorly to standard chemotherapy and is high-risk for relapse, so these survival results and reduced need for a stem cell transplant are very encouraging. Several clinical trials have investigated the use of TKI and blinatumomab as a chemotherapy-free treatment for ALL. A new phase II trial demonstrated that the chemotherapy-free regimen of ponatinib and blinatumomab may have achieved high response rates and reduced the need for an allogeneic stem cell transplant for patients with recently diagnosed Ph+ ALL.

With the development of novel, effective therapies, ALL treatment options have not only expanded, but our focus is shifting toward strategies that minimize cytotoxic chemotherapy and HSCT. With continued efforts to optimize the available therapies with novel combinations, there is reason for optimism that the treatment of adult ALL may eventually become another success story.

Brentuximab vedotin as a backbone for Hodgkin lymphoma and peripheral T-cell lymphoma

以 Brentuximab vedotin 做為何杰金氏淋巴瘤與周邊 T 細胞淋巴瘤的治療要角

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Brentuximab vedotin is a targeted therapy used in the treatment of Hodgkin lymphoma and peripheral T-cell lymphoma. It is an antibody-drug conjugate, which means it consists of an antibody attached to a chemotherapy drug. The antibody portion of Brentuximab vedotin targets a protein called CD30 that is found on the surface of cancer cells in Hodgkin's lymphoma and certain types of peripheral T-cell lymphoma. The chemotherapy drug portion of Brentuximab vedotin, called monomethyl auristatin E (MMAE), is then released inside the cancer cells, leading to cell death.

In Hodgkin's lymphoma, Brentuximab vedotin is used in several settings, including as part of frontline therapy with traditional chemo therapy ABVD for newly diagnosed patients with advanced-stage Hodgkin's lymphoma who are not eligible for or have relapsed after initial chemotherapy. Brentuximab single agent as consolidation therapy after autologous stem cell transplantation (ASCT) for patients at high risk of relapse or progression, and as salvage therapy for relapsed or refractory Hodgkin's lymphoma after failure of frontline therapy or ASCT.

In peripheral T-cell lymphoma, Brentuximab vedotin is used as front-line or in salvage therapy for patients with relapsed or refractory disease after failure of frontline therapy. It has shown effectiveness in certain subtypes of peripheral T-cell lymphoma, such as systemic anaplastic large cell lymphoma (sALCL), peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS). Brentuximab vedotin either as a single-agent therapy or in combination with other chemotherapy regimens shown promising efficacy.

By specifically targeting CD30, Brentuximab vedotin delivers the chemotherapy directly to the cancer cells, potentially minimizing the exposure of healthy cells to chemotherapy and reducing the risk of systemic toxicity. Brentuximab vedotin has generally shown a manageable safety profile in clinical trials, with adverse events that are typically consistent with its known safety profile. Common side effects include peripheral neuropathy, neutropenia, nausea, and fatigue.

The importance of treating the whole myeloma patient through optimal long-term care with Kyprolis and XGEVA

全面性治療多發性骨髓瘤患者的重要性

Chia-Jen Liu

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Multiple myeloma (MM) is a plasma cell neoplasm characterized by skeletal or bone damage due to the infiltration of bone marrow by the malignant plasma cells. Up to 80% of patients with newly diagnosed multiple myeloma develop detectable bone lesions, which result from deregulation of normal bone remodeling, thus resulting in cancer-induced bone loss and destruction and increased risk for fracture.

RANKL is an essential mediator of osteoclast formation, activation, and survival. In myeloma, RANKL is secreted by bone marrow stromal cells, osteocytes, and myeloma cells, resulting in increased osteoclast activity. Thus, excessive RANKL is correlated with increased bone disease and decreased survival in multiple myeloma. Denosumab, a fully human monoclonal antibody that binds to and neutralizes RANKL, inhibits osteoclasts and has been shown to reduce the rates of SREs not only in solid tumors but also in multiple myeloma. Synergy between bortezomib and denosumab is suggested by the fact that both affect RANKL. PIs reduce osteoclast differentiation, stimulate osteoblastogenesis and bone formation, and show bone-anabolic activity in multiple myeloma.

Second-generation PIs, carfilzomib was developed with improved efficacy and safety profiles. In contrast to bortezomib which forms a reversible complex with the proteasome, carfilzomib irreversibly binds with the proteasome. Importantly, a more patient-friendly regimen, dosing once a week instead of twice a week, seems feasible, and has recently been approved for carfilzomib therapy. As daratumumab is increasingly used as earlier in lines of treatment, carfilzomib also plays a role for treating patients with this type of relapse. In a retrospective analysis of patients with disease refractory to CD38 monoclonal antibody therapy like daratumumab, the best outcomes were observed with carfilzomib-based therapy.

Furthermore, lenalidomide and bortezomib are increasingly used as first line treatment as VRd followed by maintenance. With this treatment history, carfilzomib is more of a consideration for relapsed disease with anti-CD38 monoclonal antibody, carfilzomib, dexamethasone. Carfilzomib is a core drug in multiple myeloma therapy. Its use has evolved from single agent to doublet regimens with dexamethasone to now three drug combinations with IMiD drugs, anti-CD38 monoclonal antibodies, or cyclophosphamide. These developments have led to significant improvements in outcomes for patients, with more gains expected in the future with newer strategies that incorporate carfilzomib.

Clinical diagnosis and management of acquired hemophilia A (AHA)

後天性 A 型血友病之診斷與管理

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Acquired hemophilia A (AHA) is a rare bleeding disorder caused by increasing autoantibodies against clotting factor VIII. AHA occurs in individuals without previous history of bleeding disorders, usually elderly (median age is 70 y/o) with no gender difference. About half of AHA cases in the registry are idiopathic, and the other half of cases are associated with underlying conditions, such as autoimmune disease, pregnancy or malignancy. It often presents with spontaneous bleeding, such as hematomas, mucosal bleeding, and hemarthrosis, those are urgent and life-threatened with 15-42% of mortality rate. AHA can be challenging to diagnose, and it is essential to exclude other potential causes of bleeding. The standard test for diagnosis is the detection of a prolonged activated partial thromboplastin time (aPTT) and a decreased factor VIII activity.

The management of AHA involves inhibitor eradication and bleeding control. Immunosuppressive therapy is used to eradicate the inhibitor, and the choice of therapy depends on the severity of the bleeding and patient comorbidities. First-line therapy includes corticosteroids, while second-line therapy includes rituximab, cyclophosphamide, and azathioprine. For bleeding control, factor VIII replacement with bypassing agents is suggested and common-used, such as activated prothrombin complex concentrate (aPCC) and recombinant activated factor VII (rFVIIa). Both medications are effective for urgent bleeding control, while different treatment frequency could be considered regarding shorter half life of rFVIIa. The choice of medication depends on the underlying bleeding disorder, the patients' medical history and other individual factors.

In conclusion, AHA is a rare and severe bleeding disorder that requires prompt diagnosis and treatment. Early disease awareness and timely management of bleeding episodes are crucial to avoid severe complications. Treatment with immunosuppressive therapy and bypassing agents can eradicate the inhibitor and control bleeding, respectively. A multidisciplinary team approach involving hematologists, emergency department, gastroenterologists and obstetricians etc. is essential for optimal management of AHA.

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新冠肺炎的新知探討

Update of COVID-19

時　間：112年7月8日　　13:30~16:10

Time：July 8, 2023　　13:30~16:10

地　點：臺北榮民總醫院 致德樓第八、九會議室

Place：The Conference Room 8&9, Chih-Teh Building
Taipei Veterans General Hospital

新冠肺炎的新知探討
Update of COVID-19

Update of SARS-CoV-2 variant and diagnosis of CVOID-19

SARS-CoV-2 病毒變異株以及 COVID-19 診斷的新知

Hsin-Pai Chen

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The genetic makeup of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been undergoing continuous changes since the onset of the coronavirus disease 2019 (COVID-19) pandemic. These changes, caused by random mutations, deletions, or insertions, have resulted in the emergence of numerous variants with enhanced transmissibility and the ability to evade antibodies. Mutations, particularly in the receptor-binding domain (RBD) of the S gene, can lead to more efficient binding to host cellular receptors and evasion of antibody recognition, potentially reducing the efficacy of current vaccines. Furthermore, alterations in genetic content or protein structure can impact the accuracy of existing diagnostic tests.

To combat the spread of COVID-19, widespread access to reliable nucleic acid testing and convenient rapid antigen testing has played a crucial role. These testing methods have enabled timely diagnosis of the disease, allowing for more targeted treatment approaches and contributing significantly to pandemic control efforts. Serologic tests have also been instrumental in supporting epidemiological studies and aiding in prognostic assessments for individuals. Although various molecular, antigen, and serologic testing platforms have been developed and proven effective during the pandemic, most were designed based on the original prevalent strain of the virus during the early phase of the outbreak. However, the ongoing viral mutations raise concerns about the potential impact on the validity of currently used diagnostic tools. It remains uncertain whether these mutations will render the existing diagnostic platforms ineffective, and this is an aspect that requires careful consideration. Ongoing research and vigilance are necessary to monitor the impact of viral mutations and adapt diagnostic strategies accordingly.

Update of treatment in COVID-19

COVID-19 治療的新知

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Treatment for CVOID-19 depends on the phase of disease and consists of antiviral and anti-inflammation treatment. Recent improvement focus on the antiviral agents, and the effectiveness of current antiviral agents from real world in highly vaccinated population will be reviewed. The good news is that, currently, SARS-CoV-2 variants don't seem to be affecting the efficacy of direct acting drugs. The reason for urgency with combination therapies is the risk of resistance as we continue to use drugs by themselves. The role of combination therapy has not been defined but it may be an avenue to look at for use in immunosuppressed patients. The best treatments for pre exposure or post exposure prophylaxis are still being determined. In addition, the treatment for long COVID remains an unmet need. For anti-inflammation in severe or critical COVID-19, dexamethasone is stablished the main therapy. However, the dose or duration in fully vaccinated populations remains undetermined. We also need to determine the major variables to guide personalized treatment with steroids in critically ill patients. The addition of second immunomodulatory drug is beneficial for some patients with severe or critical COVID-19, but we need more data in fully vaccinated patients from real world. Finally, the potential for anticoagulants as a treatment for patients with severe to critical COVID-19 needs more robust data in fully vaccinated patients.

Update of COVID-19 vaccine

COVID-19 疫苗的新知

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In response to the pandemics of human infections due to SARS-CoV-2, many vaccine candidates from several platforms have been developed rapidly under rolling review process and EUA policy, including mRNA-based, vector-based, protein-based, and inactivated whole virus. Due to the possibility of shortage of international vaccine supply, Taiwan has established the programs to develop and manufacture the protein-based Covid-19 vaccine to face the threat of pandemics, in addition to purchased adenovirus-vectored vaccines and mRNA vaccines. In this lecture, I will introduce and update the step-by-step development of our domestic protein-based vaccine (MVC-COV1901), from phase I, phase II, immunobridging phase III, and placebo-controlled phase III trials, and the randomized trial for the third dosing. Furthermore, I will give the up-to-date data and review the critical publications about the Covid-19 vaccines, including the rationale of the third to fifth dose of COVID-19 vaccines especially about the impact on the fold reduction of decreased neutralizing capacity of vaccine-induced antibodies in response to the emerging variants of concern (VOC) of SARS-CoV-2, the future of heterologous prime-boost policy especially the critical roles of protein-based vaccines, the development of next-generation vaccines especially the mRNA-based and protein-based vaccines through the application of the beta variant-based S-2P, the possibility of development of universal Covid-19 vaccine development through the discovery of broad-spectrum neutralizing antibody clones, and the possible vaccine strategies to fight against emerging variants of concern with immune escape in the future.

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創新醫療在耳科學的應用

Application of Innovative Medicine in Otology

時 間：112年7月8日 13:30~17:30

Time：July 8, 2023 13:30~17:30

地 點：臺北榮民總醫院 致德樓第十會議室

Place：The Tenth Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

創新醫療在耳科學的應用

Application of Innovative Medicine in Otology

Hearing, aging, and public health: From epidemiology to public policy in the U.S.

聽力、老化和公共衛生：從流行病學到美國的公共政策

Frank R. Lin

Cochlear Center for Hearing and Public Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA

Medicine and public health have evolved through three eras over the past century. Beginning in the first half of the 20th century, infectious diseases were controlled for the first time in human history through vaccinations, antibiotics, and other strategies. Subsequently, throughout the 20th century, chronic diseases of middle and later life (e.g., cardiovascular disease, cancers) became the leading causes of mortality but have also increasingly been better controlled. These successes of public health have led to a rapidly increasing population of older adults living longer than ever before. In this third era of public health and medicine, we are now confronting the challenges of aging and how to best optimize the health and functioning of a growing population of older adults. In this era, hearing and our ability to engage effectively with the environment around us are critically important but not yet priorities in the spheres of public health and public policy.

I will discuss research over the past several years that has demonstrated the broad implications of hearing loss for the health and functioning of older adults, particularly with respect to cognitive functioning, brain aging, and dementia. I will then discuss how this epidemiologic research has directly informed and led to current national initiatives in the United States focused on hearing loss and public health. These initiatives include the Aging and Cognitive Health Evaluation in Elders (ACHIEVE) randomized controlled trial and recent enactment of bipartisan Over-the-Counter Hearing Aid regulations. Finally, I will provide some thoughts on future trends in addressing hearing loss as a public health problem and the need to develop new policies and approaches to hearing care.

Hearing loss and gene therapy: New challenges and opportunities for otolaryngologists

聽損基因療法：耳鼻喉科醫師的新挑戰與機會

Yen-Fu Cheng

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國立陽明交通大學 醫學系 耳鼻喉學科

國立陽明交通大學 醫學系 腦科所 / 臨醫所

Hearing loss is among the most prevalent congenital defects in newborns, affecting 1-2 out of every 1,000 infants with moderate to profound bilateral hearing loss, necessitating the use of hearing aids or cochlear implants. Due to the extensive use and continual advancements of genetic testing tools, more than half of congenital hearing loss cases can be attributed to genetic mutations.

Recent successes in gene therapy for various hereditary disorders have prompted researchers to explore its potential for treating hearing loss. This includes developing new gene therapy vectors and gene editing tools, which are moving hearing loss-related gene therapy research from laboratory settings towards clinical trials.

This presentation aims to discuss the recent advancements in gene therapy for hereditary hearing loss and share our research team's most recent findings in this field.

Hearing preservation with retrolabyrinthine approach for large cerebellopontine angle meningioma

以迷路後路徑保留聽力切除小腦橋腦角大型腦膜瘤

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王懋哲

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Lateral skull base surgeries for cerebello-pontine angle lesions are challenging procedures for both neurotologists and neurosurgeons. For patients with large cerebello-pontine angle lesions with poor hearing, translabyrinthine approach is the surgical approach of choice. It can provide great surgical field for both the lesion and the facial nerve, however, sacrifice of residue hearing is the drawback of this approach. For large cerebello-pontine tumors other than acoustic neuroma, mostly meningioma with useful hearing, we tried to approach these tumors with retrolabyrinthine and infralabyrinthine approach to preserve hearing.

From October, 2013 to December, 2022, 36 patients underwent retrolabyrinthine and infralabyrinthine approach for large cerebello-pontine angle meningioma. All the procedures were done by a neurotolgist and a neurosurgeon. Patients' age ranged from 27 to 74 years old. Twenty eight patients were female and the other eight were male. Tumors ranged from 3cm to 7cm in largest diameter. There are tumor with internal acoustic canal involvement in 10 patients, tumor with jugular foramen in 6 patients. Hearing was successfully preserved in 32 patients. The hearing preservation rate was 89 percent. Tumor was removed totally in 16 patients, near total removal in 10 patients, subtotal removal in 9 patients and partial removal in 1 patient. As to tumor control, only the patient with partial tumor removal required post-operative gamma knife radiosurgery for tumor control. Complications are CSF leak in 2 patients, facial palsy in 1 patient, CN6 palsy in 2 patients, CN3 palsy in 1 patient, lower cranial nerves injury in 1 patients. One patient had post- operative CVA and pneumonia. There was no mortality.

Retrolabyrinthine and infralabyrinthine approach can provide adequate surgical field for cerebello-pontine angle meningiomas. The tumor control was good. Hearing preservation can be achieved in most cases. Only one patient had deteriorated facial nerve function. The complications were acceptable. Team work is the key to this kind of surgeries.

Detection of middle ear effusion using artificial intelligence and in-ear microphones

利用耳道式麥克風與人工智慧偵測積液性中耳炎

Kuan-Chung Ting

丁冠中

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Otitis media with effusion (OME) is a condition of non-infected fluid accumulated in the middle ear space. OME, a common disease among children, may lead to hearing loss, sleep disruption, and balance issues. OME that persists for more than 3 months has the potential to cause reduced learning efficiency, signs of inattention, and delayed speech and developmental skills. The diagnostic accuracy of OME depends on clinicians' experience and evaluation tools. Assessment technologies for OME face several challenges and issues. One challenge is that these tools, such as otoscopy, rely on the interpretation of specialists. The diagnostic accuracy of otoscopes used by otolaryngologists, pediatricians, and general practitioners varies and depends on their experience and skills. Another challenge is the high cost of the equipment, for instance, digital telescope and tympanometry, which reduce its penetration rate and availability in primary clinics.

The OME detection was designed to use a machine-learning model and in-ear microphones. Two off-the-shelf microphones were placed in the bilateral ear canals to record the voice when participants pronounced five 3-second sustained vowel sounds. Various signal processing and machine learning techniques were applied to the recordings, and the magnitude spectrograms of the vowel sound recording from in-ear microphones can distinguish ears with OME from healthy ears according to the differences in high-frequency response.

Our results using in-ear microphones and ML algorithms are similar to that of typical OME detection approaches. This work demonstrates the potential to provide healthcare practitioners with a simple, safe, and more reliable expert-level diagnostic tool.

Exploring the brain abnormalities of the hearing loss individuals by the application of MRI

利用磁振造影探索聽損者的大腦

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薛健佑

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Hearing loss (HL) is the most common sensory deficit with an estimate of 2.5 billion of people affected with HL by 2050. The hearing threshold more than 25 decibel(dB) hearing level was defined as hearing loss according to the American Speech-Language-Hearing Association (ASHA) definition of the degree of hearing loss.

Magnetic resonance imaging (MRI) utilizes strong magnetic fields and magnetic gradients to create images of the human body. Functional MRI, on the other hand, measures brain activity by detecting small changes in blood flow, which correspond to changes in neural activity.

Previous studies using structural MRI have demonstrated that age-related hearing loss is independently associated with accelerated atrophy of total and regional brain volumes, as well as reduced white matter integrity. Furthermore, changes in cortical thickness of brain cortex have also been found on the aging, HL, or dementia people.

In this section, we will review recent studies that focus on brain imaging, including both structural and functional measurements, in individuals with hearing loss.

Applications of AI for hearing impairment diagnosis

人工智能於聽損診斷的臨床應用

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Hearing loss is one of the most common disabilities worldwide, and it has a significant impact on personal and public health. Patients with unidentified hearing loss are not easily detected in the early stages, which makes early intervention difficult. Detecting and treating hearing loss as soon as possible leads to better outcomes. Currently, routine pure-tone hearing screening is the best option for detecting hearing impairments. However, there are two main factors to consider when it comes to the portable device and hearing test procedures used in the routine hearing screening test.

We designed the HST audiometer for early detection of unidentified hearing impairment in children, which can replace routine hearing screening and tuning fork tests. The Hearing Scale Test (HST) uses ten stratified hearing scales from S1 to S10 for children (S1 to S15 for the elderly), with each hearing scale containing four test tones. The adjacent scales differ from each other by 5 dB, ranging from 1 dB (S1) to 71 dB (S15). The starting hearing scale of the HST is S5, which includes 1000, 2000, and 4000 Hz at 20 dB, and 500 Hz at 25 dB. The HST test reports that scales S1-S5 indicate normal hearing, scales S6 and S7 indicate possible hearing impairment, and scales S8-S15 indicate confirmed hearing impairment.

We developed an iOS application called Ear Scale App, which includes cloud monitoring and hearing detection features to assist in the diagnosis of sudden deafness in patients at TVGH. Our study confirmed a strong correlation in hearing results between conventional pure-tone audiometry and the Ear Scale app in a cohort of patients with possible SSNHL. This smartphone-based approach can be useful in clinical settings where traditional pure-tone audiometry is not available. For new patients with sudden deafness, we use the Hearing Value App for cloud-based hearing monitoring to aid in auditory rehabilitation and improve therapeutic prognosis.

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慢性肺部感染症的現況與進展

Chronic Pulmonary Infectious Diseases - Now and Future

時　間：112年7月8日　　13:30~17:30

Time：July 8, 2023　　13:30~17:30

地　點：臺北榮民總醫院 中正樓14樓胸腔部會議室

Place：14F, The Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

慢性肺部感染症的現況與進展
Chronic Pulmonary Infectious Diseases - Now and Future

Role of DST in management of NTM lung disease

非結核分枝桿菌的藥敏檢測與臨床應用

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Due to the very similar symptoms of nontuberculous mycobacteria (NTM) and tuberculosis, clinical physicians face significant challenges in diagnosis and treatment. However, there has been a growing trend of patients infected with NTM in recent years, and their serious antibiotic resistance has made treating NTM infections even more difficult. This presentation focuses on the methods of NTM species identification and drug susceptibility testing, as well as their advantages and disadvantages. Additionally, standard criteria for interpreting antibiotic resistance will be provided, which can be highly valuable for frontline clinical physicians.

Short-course therapy for latent tuberculosis infection: Now and future

潛伏結核感染的短程療法：現在與未來

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The meaning of latent tuberculosis infection (LTBI) has changed quite a lot in recent two centuries. Now, it refers to a host who is tuberculosis (TB) immunoreactive in the absence of TB disease. By treating active TB, preventing infection, and mitigating risk factors, we could possibly reduce TB burden significantly, but never eliminate it. We can only achieve that by treating active TB as well as latent TB infection. Traditionally, the effectiveness of LTBI intervention is low. Two main obstacles for implementing are being tested and complete treatment. For the latter, rifamycin-based short-course LTBI regimen offers a huge advance.

Currently, there are several therapeutic regimens for LTBI. Each has its unique characteristics and suitable patient groups. Initially shown in animal model, the effectiveness of weekly high-dose rifapentine plus isoniazid for 3 months (3HP regimen) was demonstrated in the Prevent TB trial. It has a higher completion rate, and is less hepatotoxic than traditional daily isoniazid for 9 months (9H). However, systemic drug reaction was experienced in 3.8% of 3HP cases.

As 3HP is gradually implemented in Taiwan, we experience more and more systemic drug reactions (SDR). Clinical studies revealed the association between SDR and plasma drug levels, as well as the genotypes of drug metabolizing enzymes. A population pharmacokinetic (PPK) study also revealed that a higher Cmax of isoniazid was significantly correlated with a higher risk of any adverse drug reaction. Further study using transcriptomic analysis revealed that a 3-gene signature can possibly foresee the development of SDR and can serve as a guide for establishing a safe and personalized regimen for LTBI program, facilitate Tx completion, and thus increase public acceptance of LTBI program.

To further facilitate LTBI intervention, better diagnostic tool for LTBI, shorter and more powerful regimens, cost-effective consideration in public health policy, and an adaptation of new technology in treatment supervision are necessary.

Diagnosis and treatment of invasive pulmonary aspergillosis in critical illness patients

重症病人合併侵襲性肺麴菌感染的診斷與治療

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Invasive pulmonary aspergillosis (IPA) is the most common type of fungal infection in the lungs. It primarily affects immunocompromised patients, such as those with hematologic malignancies, chemotherapy-induced neutropenia, immunosuppressive therapy, or post-organ transplantation, and can lead to sepsis and respiratory failure. It is noteworthy that IPA can also occur in critically ill patients with severe influenza or COVID-19 who are on mechanical ventilation, even if their immune function was previously normal. Due to the nonspecific initial symptoms of IPA, diagnosis can be challenging, and if the condition of severely ill intubated patients worsens under broad-spectrum antibiotic treatment, IPA should be considered as a differential diagnosis. Chest computed tomography (CT) can assist in the diagnosis of patients with immunodeficiency and new lung lesions, and the use of mycological testing methods can confirm the presence of IPA. These methods include histopathological examination of lung lesions, culture of respiratory specimens, and detection of the GM antigen in bronchoalveolar lavage fluid and serum.

In terms of treatment, when IPA is highly suspected clinically, antifungal therapy should be initiated immediately. For proven or probable IPA, triazoles such as voriconazole, isavuconazole, or posaconazole should be prioritized, while liposomal amphotericin B should be used for possible IPA to ensure broad coverage of fungal species. Combination therapy should be reserved for severe or refractory cases of IPA. Treatment should continue for 6-12 weeks, depending on the degree of immunocompromised recovery and radiographic improvement. In ICU patients with normal immune function, a shorter treatment duration of 4-6 weeks may be considered after transfer out of the ICU. This topic will provide a detailed overview of the above issues.

Comorbidities in chronic pulmonary aspergillosis and their impact on treatment

慢性肺麴菌症的好發共病症與治療考量

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Chronic pulmonary aspergillosis (CPA) is a lung infection that has gained increasing attention in recent years. It causes progressive lung damage, characterized by pulmonary cavities on imaging, and clinical symptoms including chronic cough, fever, weight loss, and even fatal hemoptysis. Unlike invasive pulmonary aspergillosis, which primarily affects immunocompromised populations, CPA usually affects those with pre-existing lung structural abnormalities due to underlying diseases such as treated pulmonary tuberculosis, non-tuberculous mycobacterial lung disease, chronic obstructive pulmonary disease, bronchiectasis, or lung cancer.

Diagnosing CPA can be challenging due to the underlying chronic lung damage caused by these pre-existing conditions. The key diagnostic indicator, aspergillus IgG, also varies in prevalence and diagnostic threshold across different regions and laboratories. Furthermore, individualized treatment for CPA, including complex drug interactions, treatment priorities, and prognostic differences, adds to the complexity of clinical decision-making. This presentation aims to provide an overview of the known and unknown aspects of CPA from diagnosis to treatment, in hopes of sparking more discussion and insight into future research directions.

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3D數位診斷上顎橫向發育不足與非手術治療之臨床新進展

Three-dimensional Digital Diagnosis and Non-surgical Treatment Approach of Maxilla Transverse Deficiency in Taipei Veterans General Hospital

時 間：112年7月8日 08:30~12:00

Time：July 8, 2023 08:30~12:00

地 點：臺北榮民總醫院 線上會議

Place：Online Meeting

Taipei Veterans General Hospital

3D數位診斷上顎橫向發育不足與非手術治療之臨床新進展

Three-dimensional Digital Diagnosis and Non-surgical Treatment Approach of Maxilla Transverse Deficiency in Taipei Veterans General Hospital

General concept and diagnosis of maxilla transverse deficiency

上顎橫向發育不足之概論與診斷

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The maxillomandibular diagnosis of orthodontic patients often is defined in three dimension, the anterior-posterior, the vertical and most easily neglected, the transverse aspect. And the deficiency in transverse dimension mostly will lead to discrepancy of vertical and antero-posterior dimension. Common etiology of transverse deficiency are cleft lip or palate, soft tissue imbalance, and excess of deficient growth of maxilla and mandible. The clinical features are posterior crossbite, dental compensation with inappropriate torque, large buccal corridors, and deepened nasolabial folds and narrow nasal base.

There are several diagnostic methods, including dental cast analysis, posteroanterior cephalograms and gradually commonly used cone-beam computed tomography (CBCT). The Yonsei transverse analysis which calculated in CBCT the difference of the width of maxilla two 1st molar and that of mandible two 1st molar gives the best diagnostic accuracy of transverse discrepancy. The norm of Yonsei index is -0.39 +/-1.87 mm in normal occlusion.

The treatment options can be divided in four parts: no treatment, camouflage, orthopedic, and orthognathic surgery. In the past, for adult patient suffering from transverse skeletal deficiency, orthognathic surgery was the only treatment method. Yet due to the advances in technique of mini-screw placement, delicate devices design, and good cooperation of dental technicians, management for transverse deficient adult patients in a non-surgical method is becoming more and more popular.

Non-surgical treatment of maxilla transverse deficiency in adults using Miniscrew-Assisted Rapid Palatal Expansion (MARPE) in TPEVGH

臺北榮總成人使用迷你骨釘輔助上顎快速擴張器治療上顎橫向發育不足之經驗

Heng-Yun Lin

林衡筠

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Background: Transverse maxillary deficiency is an issue in orthodontic treatment of adult patients. Clinical features such as deep and narrow palate, crowding, excessive vertical alveolar growth and large buccal corridors could be seen. In the past, surgically assisted rapid palatal expansion(SARPE) was the only option. However, high cost and surgical morbidity were main limitations. Miniscrew-assisted rapid palatal expansion(MARPE) was introduced in 2010s by Korean orthodontists and was widespread over the decade. Outcomes of patients in TPEVGH treated with MARPE were collected and reported.

Methods: To evaluate the dental and skeletal change of MARPE treatment, CBCT and model analysis were done before and after MARPE treatment. Measurements included of inter-molar width and inter-premolar width both at coronal(buccal cusp) level and CR(center of resistance) level. Landmarks such as ANS, PNS, paired skeletal sutures and screw position of MARPE device were also marked for measurements. Statistical analysis were performed using Paired t-tests and Spearman correlation.

Results: Our treatment outcome showed obvious skeletal effect, with an average increase about 3.34mm in maxillary inter-molar CR width. Dental effects could still be noted, with an average increase about 6.31mm in maxillary inter-molar coronal level. With small number of the samples, rest of the measurements has no statistical significance.

Conclusion: According to changes of inter-molar width and inter-premolar width, MARPE showed significant outcome in treating transverse maxillary deficient adult patient in TPEVGH. More cases may be included in the future for further research.

MARPE clinical application

迷你骨釘輔助上顎擴張器之臨床應用

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Mini-screw assisted rapid palatal expanders (MARPE) are a new type of orthodontic appliance that was introduced in recent years. The MARPE appliance can be used to expand the maxilla to create more space for teeth and improve breathing and may reduce the risk of sleep apnea. Besides, with the success of maxilla expansion, correcting posterior crossbite in adult patients, which might need surgical assisted rapid palatal expansion under general anesthesia in the past could be avoided.

The success rate of MARPE depends on various factors such as the age of the patient, the severity of the maxillary constriction, and the type of appliance used. Studies have shown that MARPE can achieve a skeletal expansion of 3-5 mm in adults with a success rate of 80-90%. However, it is important to note that success rates may vary depending on the patient's individual factors.

As with any orthodontic treatment, there can be potential complications with MARPE. Some of the possible complications include: discomfort and pain, gingival recession, screw loosening or failure, root resorption.

The technique sensitive skill on MARPE placement and current clinical applications will be introduced.

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病毒與眼睛、青光眼治療之新進展

Virus and the Eye, New Ideas in Glaucoma Management

時　間：112年7月8日　　13:30~17:30

Time：July 8, 2023　　13:30~17:30

地　點：臺北榮民總醫院 第三門診9樓創新沙龍

Place：The Clinical Innovation Center,
Taipei Veterans General Hospital

病毒與眼睛、青光眼治療之新進展

Virus and the Eye, New Ideas in Glaucoma Management

Harnessing viruses for medical unmet needs

無藥可醫時駕馭病毒

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In 2023, a severe keratitis outbreak caused by multidrug-resistant *Pseudomonas aeruginosa*, transmitted through artificial tears, occurred in the United States. When faced with infections caused by such extensively drug-resistant superbugs with no available treatments, the use of bacteriophages - viruses that specifically target and consume bacteria - can be considered for therapy. After a century since their discovery, bacteriophages have been developed into customized precision biopharmaceuticals. This talk will introduce the biological characteristics of bacteriophages and the processes of isolation, identification, cultivation, and collection. When there is a need for treatment against superbugs, the most potent bacteriophage combinations with targeted efficacy are selected through in vitro testing before administration to patients. Successful cases of infection treatment and the effectiveness of preventing nosocomial infections will be shared, along with a discussion of the challenges faced in bacteriophage therapy.

Coronavirus disease 2019 (COVID-19) perspectives

新冠肺炎面面觀

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The coronavirus disease 2019 (COVID-19) pandemic is a major global impact on human health for three years. Characteristics of aerosol transmission during latent period and highly contagious ability render the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) rapidly spreading in community. Emerging SARS-CoV-2 variant of concern, had more rapid symptom onset compared with the wild type and could be transmissible in the latent period after viral infection with highly contagious ability. The higher viral load and higher risk of pre-symptomatic transmission indicated the challenges in control of infections with the omicron variants, such as XBB-1. Breakthrough infections and re-infections by the SARS-CoV-2 variants after COVID-19 vaccination are an emerging public health issue. The continuous mutations of variants of concerns might increase in transmissibility or virulence, risk of reinfection, and decrease in the protection provided by vaccination or escape from host immunity. Moreover, waning vaccine-induced immunity and reduction of neutralizing antibodies for the variants are also probable causes of reinfection. Assessing the immunogenicity and safety of further developed vaccines is important, which might provide the chance for fighting the coming novel emerging SARS-CoV-2 variant in Taiwan. Long COVID, occurs more often in people who had severe COVID-19 illness, can include a wide range of ongoing health problems. The symptoms persisted at least four weeks after infection is the consensus of definition for long COVID. Elderly age, unvaccinated against COVID-19, underlying comorbidities and severity of COVID-19 are known risk factors for long COVID. While most people with Long COVID have evidence of infection or COVID-19 illness, in some cases, a person with Long COVID may not have tested positive for the virus or known they were infected.

Cytomegalovirus infection and ocular diseases

巨細胞病毒感染與眼部疾病

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Cytomegalovirus (CMV) belongs to the beta-herpesvirus and is an enveloped double-stranded DNA virus. Primary CMV infection usually occurs at young age. It can be transmitted from person to person by vertical transmission, by breast milk, by saliva, or by sexual contact. At times, it can be transmitted by organ transmission. Primary CMV infection may be mild or asymptomatic or with infectious mononucleosis-like symptoms. A transient viremia may occur and the virus reaches different parts of the body, including the bone marrow. When CMV infects a cell, the virus-host interplay may be lytic (such as in fibroblasts or endothelial cells) or latent (such as in myeloid progenitor cells). Viral particles can be released from infected cells during the lytic cycle but the viral genome can persist in the nucleus, expressing only a limited number of viral genes, in latent status and is difficult for the immune system to eradicate. When the host becomes immune compromised, the virus can reactivate from the latent status and causes clinical disorders.

To diagnose a CMV disease is sometimes difficult for a gap between CMV viremia and CMV disease. Quantitative polymerase chain reaction (qPCR) is a powerful tool to monitor CMV viremia. However, commercial kits for ocular lesions is in need.

CMV retinitis is the most common ocular disease, especially in the immunocompromised patients, such as patients with acquired immunodeficiency syndrome or post-transplantation. In addition, other ocular involvements such as anterior segment disease, anterior uveitis, and corneal endotheliitis have been reported. Several anti-CMV drugs, such as ganciclovir, cidofovir, and foscarnet, help to treat ocular lesions. Intra-vitreal injection of ganciclovir is preferred in order to achieve higher vitreous concentrations.

Differential diagnosis of herpetic keratitis

皰疹病毒角膜炎的鑑別診斷

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Herpetic keratitis is a common vision-threatening disease. The diagnosis is usually based on characteristic ocular manifestations. However, the manifestations are sometimes atypical because of host immunity, ocular surface condition, drug toxicity or resistance, and chronic recurrence. Also, similar presentations may be seen in keratitis due to other etiologies. For example, acanthamoebic and microsporidial stromal keratitis look similar to herpetic stromal keratitis. Initial misdiagnosis of these two corneal infections and prescribing topical corticosteroids without antibiotics may lead to poor visual prognosis. Furthermore, acute keratolysis impending perforation is seen in Sjögrens syndrome or other auto-immune diseases. Similar rapid melting of corneal stroma is also seen in herpetic necrotizing stromal keratits. The corneal condition may deteriorate more rapidly if applying topical steroids without concomitant antivirals.

Fortunately the diagnosis of herpes virus infection has become easier with the advancement of real time PCR, which should be considered in atypical cases or cases with poor response to treatment. In cases with deeper stromal keratitis but without epithelial lesions, confocal microscopy or corneal biopsy may help in the differential diagnosis.

Recently we encounter some cases with poor response to acyclovir while good response to ganciclovir. The establishment of clinically available tools to identify the resistance strains should be necessary especially in cases requiring long-term antiviral prophylaxis.

Earlier intervention for glaucoma: Using SLT and MIGS

應用雷射與微創手術於青光眼之早期介入

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Glaucoma is a progressive optic neuropathy which is the leading cause of irreversible worldwide blindness. The reduction of IOP is currently the only known modifiable risk factor. Medicine is usually the first line for the standard treatment algorithm. However, laser and surgery has been proposed for earlier intervention for glaucoma management.

Selective laser trabeculoplasty (SLT) was introduced with less destructive histopathologically, a potential benefit of repeatability and similar IOP reduction compared with traditional Argon laser trabeculoplasty. Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial showed that SLT is a safe treatment for open angle glaucoma and ocular hypertension, providing better long-term disease control than initial drop therapy, with reduced need for incisional glaucoma surgery over 6 years.

Minimally invasive glaucoma surgery (MIGS) is defined as “a type of IOP lowering device used to lower IOP using an outflow mechanism with either an ab interno or ab externo approach, associated with little or no scleral dissection and minimal or no conjunctival manipulation”. Over the last decade technologies have been developed to overcome the obstructions to restore physiological outflow. Xen gel implant (Allergan, USA) is a device which creates a drainage pathway between the anterior chamber and subconjunctival space. Previous studies have shown that Xen had a comparable IOP-lowering effect vs. traditional filtering surgery, with conjunctival-sparing, patient- friendly, and low-risk profile.

A detailed review of earlier glaucoma intervention by using SLT and MIGS will be presented.

Neuroprotection in glaucoma: Basic aspects and where are we now?

降壓以外，青光眼治療之新發展？

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Glaucoma is a progressive neurodegenerative disease that mainly affects retinal ganglion cells (RGCs) and causes axon degeneration in the optic nerve. Intraocular pressure (IOP) is a well-known risk factor in developing glaucomatous optic neuropathy. Clinically, current treatment for glaucoma remains limited to reducing IOP. However, in some patients controlling IOP is ineffective in hindering disease progression because it does not fully address the underlying vulnerability of RGCs to degeneration. Understanding the pathophysiology and possible biomolecular processes in glaucomatous optic neuropathy holds the keys to developing future therapeutic modalities that involve the survival of RGCs.

In glaucoma, neuroprotection refers to IOP-independent interventions that modulate RGCs and the microenvironment of optic nerves to promote neuron survival and maintain physiologic function. Aside from IOP, several pathogenetic mechanisms can also lead to the death of neurons, including glutamate excitotoxicity, oxidative stress, accumulation of reactive oxygen species, depletion of neurotrophic factors, ischemic change, activation of glial cells, and various genetic factors. Based on these mechanisms, numerous preclinical and clinical studies have yielded optimistic results of potential therapeutic modalities in neuroprotection for glaucoma. Although the translation from bench to bedside remains challenging, the road ahead still offers immense promise.

Pros and cons to consider while choosing premium IOL for glaucoma patients

高階人工水晶體用於青光眼病患之利與弊

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When selecting an intraocular lens (IOL) for patients with glaucoma, several important factors need to be considered. These include the potential impact on visual field testing, contrast sensitivity, and scotopic or mesopic vision. Additionally, anatomical features relevant to glaucoma patients, such as small pupils and issues with the capsular and zonular apparatus, must be taken into account to ensure optimal visual outcomes.

The use of multifocal IOLs in glaucoma patients and ocular hypertensive patients without disc or visual field damage, but who have been stable, remains a topic of debate. Multifocal IOLs can lead to a decrease in contrast sensitivity, particularly for near vision compared to distance vision, which tends to be more pronounced with refractive IOLs compared to diffractive IOLs. However, in certain cases of milder glaucoma, within reasonable limits, multifocal or extended depth of focus (EDOF) IOLs may be considered.

There were studies evaluated the outcomes of cataract eyes with glaucoma who underwent refractive multifocal IOL implantation. They reported favorable results on improvement of visual acuity. Contrast sensitivity in these eyes was comparable to that of healthy individuals. Spectacles for distance vision were not required by any patient, although a small percentage required them for near vision. Careful selection of cases for sectorial refractive multifocal IOL implantation can be effective in managing cataract eyes with glaucoma. In contrast, several studies have shown that multifocal IOLs may result in reduced visual sensitivity indices observed in automated visual field perimetry. Due to the limited scientific evidence from large trials on the impact of multifocal IOLs in glaucoma, decisions regarding their implantation in glaucoma patients should be based on individual patient motivation and the rate of glaucoma progression.

Managing glaucoma patients with ocular surface diseases

青光眼的治療如何兼顧青光眼病患之眼表健康？

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Reduction of intraocular pressure (IOP) is the only proved way to slow the rate of glaucoma progression, which is achieved by long-term topical medication in many patients. The accumulative effect of medication and preservatives result in ocular surface disorders (OSD). OSD is therefore quite common in glaucoma patients, which may affect patients' quality of life, the compliance in medication usage, and the success rate of consequent filtering surgery. All can lead to inadequate disease control and increase the likelihood of glaucoma blindness.

Glaucoma related OSD involves both aqueous deficiency and meibomian gland dysfunction (MGD), and relates to a vicious self-perpetuating cycle of inflammation. While dealing glaucoma patients with OSD, the key is to minimize the effect of glaucoma therapy on the homeostasis of the ocular surface. This can be achieved by simplify glaucoma regimen, switching to preservative-free regimen, or adopting laser or minimally invasive glaucoma surgery to achieve adequate IOP reduction. On the other hand, the OSD can be addressed and treated by adding preservative-free lubricants, anti-inflammatory treatment, and treatments for MGD. Our preliminary study revealed that Intense Pulsed Light is effective in ameliorating symptoms and signs of MGD in glaucoma patients after prolonged topical glaucoma medication, although the effect lasted shorter than that in non-glaucoma patients. Early recognition of glaucoma medication related OSD with timely modification of glaucoma treatment may improve ocular surface healthy, IOP control and patient satisfaction.

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局部治療在泌尿惡性腫瘤的運用

Focal Therapy for Urological Cancer

時　間：112年7月8日　　13:30~17:30

Time：July 8, 2023　　13:30~17:30

地　點：臺北榮民總醫院 第三門診大樓九樓創意谷

Place：The Clinical Innovation Center
Taipei Veterans General Hospital

局部治療在泌尿惡性腫瘤的運用
Focal Therapy for Urological Cancer

The new strategy in high-intensity focused ultrasound (HIFU) therapy for prostate cancer: HIFU basic theory, clinical application, and CGMH's experience sharing

高聚焦超音波消融 (HIFU) 治療攝護腺癌的新策略：HIFU 基礎原理，臨床的應用及長庚醫院的經驗分享

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Introduction: HIFU Basic theory

HIFU is a treatment that uses high frequency ultra-sound waves to destroy prostate cancer cells. The waves create heat that destroys the cancer cells without creating wound or invasive way.

Clinical application

Many institutes recommend using HIFU for prostate cancer in specific stages or as part of clinical trials to improve healthcare.

CGMH's experience sharing

In the 82 analyzed cases, mean age was 67 years (95% confidence interval 66–69), and mean preoperative prostate-specific antigen was 6.4 ng/cc (5.5–7.4). Histology of PCa up to Gleason 8 (4 + 4), whereas no limitation in terms of Gleason score. Regarding early complications, low-grade Clavien–Dindo I–II were reported in 26% (16–37), whereas high-grade Clavien–Dindo III were found in 3.8% (0–8.6).

Conclusion: This preliminary analysis of the result of focal HIFU treatment of PCa in our institute shows promising oncologic and functional outcomes. Well-selected patients may be candidates for such a conservative partial treatment of the gland. Well-designed prospective trials are awaited to compare HIFU focal treatment with current standard of care.

Preliminary experiences of high intensity focused ultrasound treatment for prostate cancer in Taipei Veterans General Hospital

高能聚焦超音波治療攝護腺癌 - 臺北榮總的初步經驗

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Background: Prostate cancer is one of the most common malignancies affecting men worldwide. Traditional treatment options such as surgery and radiation therapy carry significant risks and potential side effects. High Intensity Focused Ultrasound (HIFU) has emerged as a promising non-invasive alternative for localized prostate cancer treatment. This study aims to present the preliminary experiences of HIFU treatment for prostate cancer at Taipei Veterans General Hospital, evaluating its initial efficacy in a real-world clinical setting.

Methods: A retrospective analysis was conducted on patients diagnosed with localized prostate cancer who underwent HIFU treatment at Taipei Veterans General Hospital between June 2022 and June 2023. Patient demographics, preoperative prostate-specific antigen (PSA) levels, Gleason scores, and clinical stages were collected. The HIFU procedure involved precise and targeted delivery of ultrasound energy to the prostate, guided by real-time imaging. Procedural details, including treatment duration, complications, and adverse events, were documented. Post-treatment follow-up included regular monitoring of PSA levels and imaging studies to assess treatment response.

Results: A total of 5 patients with localized prostate cancer were included in the analysis. The mean age of the patients was 74 years (range 55-83). The mean pre-HIFU PSA level was 9.41 ng/mL (range 0.51-19.40), with Gleason scores ranging from 6 to 8. HIFU treatment was successfully performed in all patients. The T stage on pre-HIFU MRI was T3a in 3 patients, T2c in 1 patient, and no visible cancer foci in 1 patient. No major complications were encountered during or immediately after the procedure. At a median follow-up of 8 months (range 3-12), the mean PSA level decreased to 1.64 ng/mL (range 0.02-5.93), indicating a significant reduction in disease burden. Imaging studies showed localized tumor control in 60% of patients, and there was no evidence of disease progression in any patient.

Conclusion: In this preliminary experience of HIFU treatment for prostate cancer at Taipei Veterans General Hospital, HIFU demonstrated promising safety and efficacy in the management of localized disease. The procedure was performed successfully without major complications, and patients experienced a significant reduction in PSA levels and localized tumor control. Further long-term follow-up and larger-scale studies are warranted to validate these preliminary findings and establish HIFU as a viable treatment modality for prostate cancer.

Foco-regional cryotherapy for target lesion of prostate cancer

局部區域性冷凍治療應用於攝護腺癌之標的病灶

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For patients with elevation of prostate-specific antigen (PSA) who might be suspicious of prostate cancer, multi-parametric magnetic resonance imaging (mpMRI) has been an alternative choice beside the direct random biopsy. If there is a lesion suspected in the mpMRI, such as that of Prostate Imaging–Reporting and Data System (PI-RAD) score 4 or 5, mpMRI-fusion targeted biopsy would therefore be suggested. Since the targeted biopsy is feasible for this kind of scenario, targeted treatments including foco-regional cryotherapy are reasonably considerable, especially for those with localized prostate cancer of low or favorable intermediate risk.

While a radical surgery remains the mainstream treatment for localized prostate cancers, focal therapies could still be an alternative choice for those who are ineligible for radical prostatectomy (RP). Although cryotherapy has been one of these options for a long period of time, the whole-gland cryotherapy might lead to urethral stricture in a certain proportion, even with a urethral warmer all along the procedure. However, since active surveillance (AS) is also suitable for localized prostate cancer with low or favorable intermediate risk, foco-regional cryotherapy could bring a new pathway between AS and RP.

On the other hand, for patients with local diseases who had been treated with radiotherapy and developed biochemical recurrence, salvage RP is still an alternative choice but also possibly brings complications to a certain degree. Therefore, foco-regional cryotherapy could also be provided as another option regarding salvage treatments, particularly with the aid of prostate-specific membrane antigen (PSMA) scanning. If the detectable or viable lesion is still within the prostate capsule as a local disease, PSMA-directed cryotherapy after radiotherapy is also safe and feasible, after a targeted biopsy according to the PSMA image.

So far there have been seven patients who had received foco-regional cryotherapy in Taipei Veterans General Hospital, either as a primary treatment for a localized prostate cancer of low or favorable intermediate risk, or as a salvage therapy after radiotherapy for a local disease. All patients have taken regular follow-up, with a stable serial PSA and no visible recurrence by mpMRI annually. Here we present the preliminary results concerning foco-regional cryotherapy in circumstances as mentioned above.

The current status of cryoablation in primary renal cell carcinoma

冷凍治療在原發性腎細胞癌的近況

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Cryoablation is one of the thermal based ablations. The origin of the cryoablation can be traced back the 1800s and was used to treat advanced carcinomas of the breast and uterine cervix with iced saline solutions. The mechanism of the cryoablation can be separated to direct effect and indirect effect which changes the cellular microenvironment and impair tissue viability.

There are several advantages of percutaneous cryoablation, including less invasive, less painful, less damage to collagenous tissue, clear visualization of the ablation zone, flexibility etc. Currently the absolute contraindication for cryoablation is coagulopathy. As for RCC, the relative contraindication for cryoablation is Stage ≧ T2.

Current society clinical practice guidelines on small renal masses including AUA, EAU, NCCN and CIRSE suggested for T1a RCC: Suggest the use of thermal ablation in select patient groups. Of the techniques available, only RF ablation and cryoablation are specifically mentioned in select guidelines as for T1b the suggested not directly address the use of ablation. The EAU currently recommends PN over RN, whereas the NCCN states that either PN or RN is acceptable.

As for recent experience in VGHTPE, the total postoperative complication rate showed no significant between PC group and PN group. No significant difference in overall survival and cancer specific survival between two groups. The local recurrence free survival is less in cryoablation group. All with similar result compared with other studies

Cryoablation is proven to be a safe and effective alternative treatment for cT1a RCC in selected patients. In high-risk patients with T1b RCC who are not surgical candidates, percutaneous thermal ablation may be an appropriate treatment option; however, further research in this area is required.

Imaging diagnosis and ablation therapy of recurrent RCC

腎細胞癌復發的影像診斷與局部消融治療

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Recurrence of renal cell carcinoma (RCC) after surgery is not uncommon. Approximately 30% of patients have metastatic disease at time of RCC diagnosis, usually at multiple sites. Twenty five percent of patients developing metastatic disease following nephrectomy with curative intent. Within the metastatic RCC patient group, only 3% have solitary metastasis. Common sites of metastasis include lung, bone, lymph node, liver and adrenal gland. It is worth noticing that those with late recurrence (> 5 years) have significantly longer median overall survival as compared with those with early recurrence (56 months vs 36 months; $P < 0.0001$). The results may imply that late recurrence deserves aggressive intervention, especially for oligometastatic status. Aggressive local control of oligometastasis may yield systemic control. Another pattern of RCC recurrence is synchronous/ metachronous RCC in other parts of kidney. The mean time to appearance of metachronous lesion is 62 ± 41 months (range 9–149 months), can be a decade. The incidence for metachronous renal tumor is cumulative over time.

Cryoablation is a minimal invasive surgical technique has been proved to be an effective and safe treatment for many locations of oligometasis, including but not limited to hepatic, pulmonary, musculoskeletal, retroperitoneal nodal metastasis, pelvic side wall disease. It is a less invasive treatment as compared to surgical lymphadenopathy, and the procedure is repeatable. Cryoablation could also be applied on those patients with radiation failure since cryoablation and radiotherapy have different mechanism.

In this presentation, we will review the imaging appearance of RCC recurrence, as well as the technique and consideration of focal ablation therapy.

Robot-assisted partial nephrectomy for renal cell carcinoma: The experience of Taipei Veterans General Hospital

以機器手臂部分腎臟切除手術治療腎細胞癌：臺北榮總的經驗

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Background: Robot-assisted partial nephrectomy (RAPN) has become the standard of care for clinical T1 renal tumor. We reported the experience of RAPN for renal cell carcinoma (RCC).

Methods: We have performed 659 RAPNs in 653 patients since the establishment of the first da Vinci Surgical System at our institute till November 30, 2022. Six patients had bilateral renal tumors. We prospectively collected preoperative baseline demographic data and perioperative data. The follow-up data, including local recurrence, distant metastasis, and renal function were extracted from the medical record of each patient.

Results: We successfully performed 651 (98.8%) RAPNs. Eight RAPNs were converted to radical nephrectomy. The mean age of these patients was 57.1 ± 13.1 years old. The mean maximal tumor diameter as measured by preoperative CT scan was 4.1 ± 2.1 cm. The mean console time was 207.1 ± 74.5 minutes. The mean blood loss was 266.1 ± 335.7 mL. The blood transfusion was needed in 50 (7.7%) patients. The mean warm ischemia time was 25.7 ± 15.7 minutes. The mean postoperative hospital stay was 5.4 ± 1.7 days. The overall postoperative 90-day complication rate was 17.2% and the major complication rate (Clavien-Dindo grade III or higher) was 4.5%. There were 467 (71.7%) RCCs which were composed of stage pT1a in 316 (67.7%), pT1b in 79 (16.9%), pT2a in 6 (1.3%) and pT3a in 66 (14.1%). All surgical margins were negative. During the follow-up period (49.8 ± 39.5 months), there was 6 (1.3%) local recurrence and 10 (2.1%) distant metastases. The 5-year overall survival (OS), cancer-specific survival (CSS) and disease-free survival (DFS) rates were 94.4%, 98.0% and 97.5%, respectively. The 10-year OS, CSS and DFS rates were 89.2%, 98.0% and 87.3%, respectively.

Conclusion: RAPN is a safe and effective treatment for clinical localized RCC.

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台灣醫院整合醫學與醫學教育之發展現況與未來展望

Current Development and Future Prospective of Integrated Medicine and Medical Education in Taiwan

時　間：112年7月8日　13:20~17:30

Time：July 8, 2023　13:20~17:30

地　點：臺北榮民總醫院 長青樓護理館會議室

Place：Nursing Arts Laboratory, Evergreen Building, Taipei Veterans General Hospital

台灣醫院整合醫學與醫學教育之發展現況與未來展望

Current Development and Future Prospective of Integrated Medicine and Medical Education in Taiwan

What's the impact of transition healthcare: From the past of evidence-based retrospective experience to the future prospective

轉銜照護可以帶來什麼：以實證醫學回溯過去經驗到未來展望

Yen-Po Tsao

曹彥博

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臺北榮民總醫院 內科部 全人整合醫學科

Transition healthcare has been conducted from Ministry of Health and Welfare for several years, and the development of it varied a lot in different hospitals. The diversity of transition care reflects the transition healthcare could be adapted in medical care depending on the scenario and needs in healthcare system. We will retrospectively acquire the experience of transition care from Taiwan and other countries through evidence-based medicine to demonstrate the impact of transition medicine from different aspects. Besides this, we will share the experience in Taipei Veterans General Hospital to propose the future prospective of transition healthcare, hoping to integrated novel technology in renovation of healthcare beyond traditional medical care.

The strategy of stratified healthcare of cancer patients: The experience from Patient-centered Seamless Transition and Referral System (P-STARs) in NTUH

癌症照護的分級策略：臺大醫院星月計畫轉銜經驗

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曾家琳
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臺大醫院 家庭醫學部

The main target of medical care is the emergent, critical, difficult and rare diseases in medical center, especially the treatment of cancer. Owing to the lack of restricted referral care system or family physician-based care, cancer screening and cancer terminal care were mostly conducted in medical center, which lead to the overload of system and reduce the care quality. From 2019, Patient-centered Seamless Transition and Referral System (P-STARs) in NTUH linked different levels of medical care network, from cancer prevention, screening, to terminal cancer care through stratified care system. Within these 4 years, we gradually established the transition education, transition consultation, transition from site-to-site, and public propagation for transition healthcare in cancer patients.

The continuous integrated healthcare model: From acute to community care

連續性之整合照護模式：從急性醫療至社區照護

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蔡岡廷
Center of Integrative Medicine, Chi Mei Medical Center, Tainan, Taiwan, ROC
奇美醫院 整合醫療中心

Taiwan has high a quality healthcare system with world-class emergency and critical care. Frail elderly patients have multiple chronic diseases with deteriorated life function, which could not be simply relieved one disease and improve their overall conditions. The progressively longer admission time, higher re-hospitalization rated, and lower the medical care points reflect that we shall face these problems through a comprehensive aspect. Based on the characteristics of the elderly, the new era of medical care system will focus more on the continuity, preventability, and team-based operation to respond the healthcare problems and life issues of patients. Because of the continuous healthcare mode, the location shall not be restricted in hospital but extension to the home of patients. We need a holistic integrated model to link current healthcare system and home care to flexibly respond to the change of healthcare due to the aged society.

Standardized patients in problem-based learning curriculum Department of MacKay Medicine experience sharing: Challenge and opportunities

標準化病人在馬偕醫學系問題導向課程經驗分享：挑戰與發展

Tsang-En Wang

王蒼恩 林肇鋒 吳懿哲 李朝雄 周逸鵬

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馬偕醫學院 醫學系

Problem-based learning (PBL) originated at McMaster University in Canada. Half a century later, this teaching method is still widely used all over the world. It has its own characteristics. However, with the changes of the times, even if the basic spirit of PBL remains unchanged, the implementation methods will naturally adapt to local conditions. In the past, PBL teaching cases were all paper. Over the years, many instructors have experimented with incorporating other media such as audio recordings of actual patients, video clips, and even developing virtual interactive patients. These efforts all hope to improve the effectiveness and orientation of PBL courses.

A few years ago, the Department of Medicine of Mackay Medicine College and the Department of Medicine of National Yang Ming Chiao Tung University tried to introduce standardized patients (SPs), or hybrid paper cases into the PBL curriculum and published this experience in AMEE. Today's report is mainly to share the concept, experience, and method of introducing SPs in the 4th-grade PBL course. Moreover, we take this opportunity to discuss the challenges of SP in PBL reform teaching, barriers of writing cases, tutors training, SP training to classroom performance, and required resources. At the same time, we discuss the development of such teaching in the future also.

Integrating standardized patients in problem-based learning tutorial: Experiences of National Yang Ming Chiao Tung University

標準化病人應用於 PBL 教學：陽明交通大學經驗分享

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張景智

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Problem-based learning (PBL) has been widely adopted in medical education. However, its application for medical competences of future doctors has been questioned due to the lack of interaction with a real patient. Standardized patients (SPs) might solve this problem. SPs are volunteers with various backgrounds who participate actively in the teaching and evaluation of medical students. After appropriate training, they can show different clinical scenarios preciously and repeatedly. In National Yang Ming Chiao Tung University, we integrates SPs in PBL tutorial for 5 years. Both SPs and tutors think that medical students participate actively and are competent in this program. A lot of students agree that this program significantly inspires their learning motivation, increases confidence level in interviewing patients and encourages critical thinking. A majority of SPs, tutors and students agree that this design enhances the motivation of students and supports such an application in PBL tutorials.

Practice of training clinical reasoning as “Give Me Five” model in medical education

演練 Give Me Five 模式訓練醫學教育中臨床推理能力

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蔡依霖

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臺北榮民總醫院 內科部 一般內科

The capability of applying clinical reasoning is pivotal for the clinical practitioner to make right decision according to the condition of the patient. This is not born-to-be and cannot be learned merely from textbooks. Instead, it should be cultivated by training and practicing, especially the capability of making differential diagnosis. In order to strengthen the clinical reasoning capability in medical students upon their bridging from medical school to clinical setting, the Division of General Medicine, Taipei Veterans General Hospital developed the “Give Me Five” interactive clinical reasoning training model. It invites the young doctors to be the standardized patients to simulate the scenario of clinical condition for other trainees to give rise to five reasonable differential diagnosis, then arranging feasible tests and image studies according to the differential diagnosis. This training model has been proved to be helpful in promoting the skills in the aspect of history taking of mini-CEX. In addition, those who played the role of standardized patients had higher scores in different aspects of mini-CEX than those who did not. These encouraging findings have led to the collaboration between us and the National Yang Ming Chiao Tung University, which applied the spirit of early clinical reasoning training to medical education, allowing the medical students to understand and practice clinical challenges earlier.

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免疫細胞治療新進展學術研討會

International Symposium on New Advances in Immune Cell Therapy

時 間：112年7月9日 08:00~12:30

Time：July 9, 2023 08:00~12:30

地 點：臺北榮民總醫院 致德樓第一會議室

Place：The First Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

免疫細胞治療新進展學術研討會

International Symposium on New Advances in Immune Cell Therapy

Development of immune therapeutics targeting pancreatic ductal adenocarcinoma utilizing genetic engineering and reprogramming strategies

結合基因修飾及重新編程策略開發胰臟癌免疫治療技術

Chia-Ning Shen
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中央研究院 基因體研究中心

Recent developments in cell-based immunotherapies have revolutionized the way to treat cancer. Chimeric antigen receptors (CAR) are genetically engineered receptors that can recognize specific antigen and activate downstream signaling. CAR-T cell therapies have been recognized as an effective therapeutic strategy to eliminate hematologic malignant cancers and to autoimmune diseases such as systemic lupus erythematosus. Nevertheless, successes in solid tumors such as pancreatic ductal adenocarcinoma (PDAC) have been limited. Our current work showed patients with PDAC expressed both CD318 (also known as CUB domain-containing protein 1 (CDCP1)) and EGFRvIII (deletion of exons 2–7 in EGFR that constitutively activates downstream signaling to promote tumor growth). In collaboration with Professor Han-Chung Wu, novel anti-EGFRvIII and anti-CD318 monoclonal antibodies have be generated and utilized to EGFRvIII and CD318-CAR-T lines which exhibited activity against PDAC cells. As lower persistence of CAR-T cells and decreased fitness of T cells in the immune suppressive-microenvironment of PDACs are thought to be the key barrier affecting therapeutic efficacy CAR-T cells. Since natural killer (NK) cells can recognize and eliminate cancer cells and possess the capability to stimulate adaptive immune responses either via secreting cytokines or direct interacting with T cells, we have established methodologies to produce iNK cells from induced pluripotent stem cells and utilized iNK cells to enhance efficacy of CAR-T cells against PDACs. Hopefully, the current findings can lead to develop solutions to overcome technical barriers of CAR-T cell therapy in PDACs.

New advance of immune mediated cell therapy and microbiome in cancer treatment

免疫細胞治療及微生態在癌症治療的新進展

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吳登強

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高雄醫學大學

In recent years, extensive research has focused on the relationship between the gut microbiota and cancer. Accumulating evidence reveals the crucial role of the microbial community in defining the efficacy and toxicity of cancer treatments. Dr. Koh's research team made a significant discovery that certain bacteria in the gut microbiota, such as Bacteroides spp. and Burkholderiales spp., can translocate to other organs. This translocation promotes the activation and proliferation of T cells, enhancing systemic anti-tumor immune responses.

A study conducted at UPenn further confirmed the impact of compositional differences in the gut microbiota, antibiotic treatments, or heterologous fecal microbiota transplantation on Adoptive Cell Transfer (ACT) therapy in tumor-bearing mice. The study demonstrated that depleting bacteria using vancomycin increased systemic CD8α+ DCs, which sustain tumor-specific T cells in an IL-12-dependent manner. As a result, tumor growth in mice was reduced. Conversely, treatment with neomycin and metronidazole showed no effect, highlighting the specific role of gut microbial communities in host responses.

Dr. Kenya Honda published a study in an international journal, indicating that co-colonization of 11 strains of bacteria isolated from healthy human feces in the gut effectively induces IFN-γ-producing CD8 T cells in the mouse intestine and other organs without causing inflammation. This induction enhances the host's resistance to Listeria monocytogenes infection and augments the efficacy of immune checkpoint inhibitors in a syngeneic tumor model l. The gut microbiota can be easily modulated through various strategies, including fecal microbiota transplantation (FMT), probiotics, and the use of specific antibiotics. Preclinical studies have elucidated the mechanisms by which the microbiota influences cancer treatment outcomes, and clinical trials have demonstrated the potential of microbiota in modulating cancer therapies, making them a promising and widely effective biological therapeutic approach.

It is worth noting that recent research has shifted attention to bacteria-mediated synergistic cancer therapy (BMSCT), which combines microbiota-based therapies with different conventional anticancer treatments such as chemotherapy, photothermal therapy, reactive oxygen and nitrogen species therapy, immunotherapy, or prodrug-activating therapy. The unique characteristics of microbiota, including tumor-targeting specificity, high motility, immunogenicity, and their ability to serve as gene or drug carriers, have led to the utilization of several types of bacteria in the treatment of solid and metastatic tumors. With the development of synthetic biology, engineered and modified microbes have been endowed with controlled expression of therapeutic proteins. Additionally, they are utilized for targeted drug delivery, photothermal therapy, magnetic hyperthermia, and photodynamic therapy, effectively enhancing the anti-tumor efficiency of synergistic cancer therapies."

Tiny vesicles, huge impact: The application of extracellular vesicles in cancer immunotherapy and regenerative medicine

微小囊泡，巨大影響：細胞外囊泡在腫瘤免疫治療和再生醫學中的應用

Shinn-Zong Lin

林欣榮

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佛教慈濟醫療財團法人花蓮慈濟醫院

Exosomes, the extracellular vesicles secreted by various cells, have diverse biomolecules that modulate cellular functions in recipient cells.

Tumor-derived exosomes play the pivotal role in transferring oncogenic molecules to neighboring cells, leading to the alteration of their phenotype and promoting tumor growth, metastasis, drug resistance, and modulation of tumor microenvironments. Our research on malignant brain tumors has revealed that glioblastoma stem cells (GSCs) transfer their cargoes to tumor non-stem cells or normal cells via extracellular vesicles (EVs), leading to the development of a tumor stem cell subtype with therapeutic resistance and cancerous properties. TZAB-001, a monoclonal antibody produced from GSCs-derived extracellular vesicles, significantly reduce the therapeutic resistance of tumor stem cells by blocking the intercellular propagation of EVs. The TZAB-001 recognized proteins expressed in gliomas almost 60 times higher than other tumors. Immunohistochemical staining and western blot show that TZAB-001 antibody specifically recognizes human GBM stem cells, liver cancer cell line HepG2, pancreatic cancer cell PANC-1, and lung cancer cell line A549, but not normal brain cells. The results reveal that TZAB-001 has the application potential for tumor diagnosis, CarT immunotherapy in cancer stem cells, and ADC drug development to enhance their efficacy.

In regenerative medicine, exosomes derived from stem cells have shown promising results in promoting tissue repair and regeneration. Furthermore, exosomes also modulate the immune response and promote angiogenesis, which are critical processes for tissue regeneration. Our studies in Alzheimer's disease focus on developing a culture medium which can increase the exosomes production. Using mesenchymal stem cells (MSCs) and Trisomy-derived T21 AF-iPS cells co-culture system, we identify an exosome enhancer TZX4 that can significantly increase the production of exosomes. In addition, TZ-008 exosomes selected by small molecule BP, which significantly increase the production of the cytokine IL-34 to aid in treating Alzheimer's disease while reducing inflammatory cytokines such as IL-6 and IL-8. Furthermore, TZ-008 exosomes can directly reduce the production of amyloid beta proteins that lead to Alzheimer's disease.

The application of exosomes in regenerative medicine and cancer holds great promise. Nevertheless, there are still many challenges that need to be overcome. These include optimizing the isolation and characterization of exosomes, understanding their specific functions and mechanisms of action, and developing effective delivery strategies for clinical applications. Further research in these areas is needed to fully realize the potential of exosomes as a new class of therapeutics.

Regenerative medicine: From cell, exosome, to allograft

再生醫學：從細胞、外泌體到異體移植

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義大醫院

Olfactory ensheathing cell (OEC) transplantation has been trialed as a promising SCI treatment. Extracellular vesicles (EVs), which regulate cell-cell interactions, have recently garnered extensive research interests and emerged as a non-cell based therapy in neurological disorders, including in SCI animal models. However, there have been no reports of human OEC-EVs and their beneficial effects on neuron regeneration. Here, we investigated the effects of EVs isolated from human OEC on the viability of neuronal cells. EVs were isolated from primary human OECs (hOECs) by serial ultracentrifugation. The hOEC-EVs were characterized by transmission electron microscopy, western blotting, and nanoparticle tracking analyses. We conducted CCK8 and lactate dehydrogenase assays to assess the cell proliferation and cytotoxicity of neural progenitor cells (NPCs) exposed to hOEC-EVs. Tert-butyl hydroperoxide (t-BHP) was utilized to mimic oxidative stress-induced cytotoxicity in NPCs. The modal diameter of hOEC-derived EVs was 113.2 nm. Expressions of EV markers such as CD9, CD63, and CD81 were detected by western blotting. hOEC-derived EVs enhanced the proliferation of NPCs and ameliorated cell cytotoxicity mediated by t-BHP. Our findings reveal a role for hOEC-derived EVs in NPC proliferation and oxidative stress-induced neuronal toxicity model. We also investigated the mRNA profiling in OEC-EV which indicated a rational approach to the functions of NPCs. These results may be useful for developing non-cell therapy OEC-EV-based treatment in spinal cord injury and acquired nervous system disease.

Using MSC for knee cartilage defect and OA treatment: From clinical trial to regulations of special medical techniques

幹細胞用於軟骨缺損及退化性關節炎：臨床試驗與特管辦法

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亞東紀念醫院

Cartilage defect is a challenging problem for orthopedic surgeon. Once the cartilage had been destroyed it cannot be repaired without intervention. Traditionally microfracture and Mosaicplasty had been used for the treatment. In the last two decades, cultured chondrocytes had been developed for treatment of cartilage defect. First human report for ACI was published in 1994. Later more and more research had been performed including mesenchymal stem cells (MSC).

Taiwan's orthopedic surgeons also gave lots of efforts in regenerative research of cartilage defect treatments. In this lecture, we will briefly introduce our efforts of development of tissue engineered cartilage from bone marrow mesenchymal stem cells, and the translation medicine study to clinical trial.

Because Taiwan's government has announced "Regulations Governing the Application of Specific Medical Technique and Medical Device" (Regulations of Special Medical Techniques) in 2018, now Taiwan has stepped into the era of regeneration medicine and cell therapy, we believe there will be more and more application in the field of orthopedic regeneration medicine.

We had also performed the first clinical trial using infra-patellar fat pad derived MSC for knee osteoarthritis (OA) treatment in the world, and had successfully get government's approval under Regulations of Special Medical Techniques. Here we will also briefly present current results.

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運動傷害治療的最新發展

Comprehensive Sports Medicine Update

時 間：112年7月9日 08:20~12:00

Time：July 9, 2023 08:20~12:00

地 點：臺北榮民總醫院 致德樓第二會議室

Place：The Second Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

運動傷害治療的最新發展
Comprehensive Sports Medicine Update

High tibial osteotomy with meniscus repair

高位脛骨截骨手術合併半月板修復

Yi-Hung Chiang

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國立陽明交通大學附設醫院 骨科

Open wedge high tibial osteotomy (OWHTO) is a well-established treatment option for medial compartment arthritis of the knee joint. This procedure can provide the medial compartment with a favorable mechanical environment for better healing of the articular cartilage by reducing the load. At the same time, medial meniscus tear is commonly observed in the osteoarthritic knee especially the posterior horn root tear. Combined performance of medial meniscal posterior root repair (MMPRR) during OWHTO has remained controversial, however, more and more research demonstrates there is a synergistic relationship between MMPRT repair and knee realignment, resulting in improved knee biomechanics for meniscal root healing and cartilage protection. The standard procedures for MMPRT include pull out suture repair and suture anchor fixation. There are some tips for pull out suture repair to avoid interference between locking screws and tibial tunnels. Because it could lead to suture damage in pull-out repair. Further, insufficient screw insertion could lead to inferior stability of plate fixation. Finally, according to the recent systemic review, repair of the MMPRT during OWHTO showed a superior healing rate to the unrepaired MMPRT. However, repair of the MMPRT was not related to the postoperative radiologic and clinical outcomes.

Arthroscopic all inside wrapping repair for lateral meniscus bucket handle tear

關節鏡包裹式縫合治療外側半月板桶柄狀撕裂

Kun-Hui Chen

陳昆暉

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臺北榮民總醫院 骨科部

Background: To evaluate the clinical and radiographic healing rate of All Inside Wrapping repair of Lateral Meniscus Bucket Handle Tears.

Methods: Retrospective review of patients with lateral meniscus Bucket handle tear that underwent all inside wrapping repair between 2012 to 2021 in our institution, with an average of 2 years follow up. At six month postoperatively all patients had MRI performed, and healing was evaluated by Henning's criteria. Post operative clinical outcome was evaluated by IKDC score.

Results: In total 34 patients underwent this procedure. Clinical healing was seen in 32 patient, and 2 patient had meniscectomy performed. Complete radiographic healing was seen in 22 patients, and 8 patients only showed partial radiographic healing. Failure to heal on MRI was seen in 3 patients, none of which required a meniscectomy. The post operative IKDC score was 83.7.

Conclusion: LMBHT repaired with all-inside wrapping technique has a 94.1 % clinical healing rate.

However 6 month post operative MRI showed 66.6% radiographic healing, 24.2 % partial healing and a 9 % failure to heal according to Hennings criteria. The all inside wrapping technique is effective and safe for the treatment of bucket handle tear of the lateral meniscus.

Arthroscopic all-inside double vertical cross-suture technique for lateral meniscus radial tear

關節鏡雙股交叉縫合治療外側半月板放射狀撕裂

Shih-Han Yeh

葉詩翰

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臺北榮民總醫院 骨科部

衛生福利部立桃園醫院 骨科部

Background: Repairing meniscus tears in avascular areas is challenging. A complete radial tear, which runs radially from the central area to the periphery, is the most difficult tear to repair and often lacks the vascular supply necessary for healing. The purpose of this study was therefore to assess failure rate and patient clinical outcomes following arthroscopic all-inside double vertical cross-suture of lateral meniscus complete radial tears.

Methods: We retrospectively reviewed records of 27 patients who underwent all-inside double vertical cross-suture radial tear repair of the lateral meniscus at our institute between 2011 and 2018. Six months postoperatively, the meniscus healing and extrusion status were evaluated through magnetic resonance imaging. Preoperative and postoperative knee function, measured through IKDC, Lysholm knee, and Tegner activity scale scores, were compared

Results: The preoperative mean (standard deviation) IKDC score, Lysholm knee score, and Tegner activity scale scores were 53.4 ± 5.3, 63.2 ± 9.3, and 4 ± 0.7, respectively. At the last follow-up (≥24 months postoperatively), these scores increased to 92.1 ± 2.6, 90.8 ± 4.2, and 6.1 ± 1.3, respectively (all ($p < .05$). Complete healing of the meniscus was observed in 23 patients, and 4 patients had meniscus retear or nonhealing. The overall healing rate was 85.2%. No significant differences were noted in healing rates between those with isolated radial tears (87.5%) and those with combined ACL rupture (84.2%; $p = .826$) nor in progression of coronal and sagittal meniscus extrusion ($p = .133$ and .797, respectively).

Conclusion: In patients with complete radial tears of the lateral meniscus, using an arthroscopic all-inside double vertical cross-suture repair technique results in improved functional outcomes and activity levels as well as a high healing rate without progression of meniscus extrusion. This is the first clinical study to report the use of all-inside double vertical cross-suture to repair a complete radial tear. For the repair of radial tears of the meniscus, the all-inside double vertical cross-suture technique is effective and safe.

ACL reconstruction : Standardization or customization?

前十字韌帶重建手術 - 標準化抑或是客製化？

Hsuan-Hsiao Ma

馬瑄孝

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Anterior cruciate ligament (ACL) reconstruction surgery is a common knee surgery that has become increasingly standardized over the years. Through years of clinical practice and research, ACL reconstruction surgery has become more standardized with clear steps and practices. There are some of the standardization practices for ACL reconstruction surgery, such as patient evaluation, surgical approaches (such as artificial ligament or autograft, tunnel position, and graft fixation), surgical instruments/materials, and postoperative care and rehabilitation.

However, as every patient is unique, the surgeon must choose the most appropriate surgical approach and treatment plan based on the patient's individual condition. Thus, customization of ACL reconstruction involves tailoring the surgical technique and postoperative rehabilitation to meet the individual needs and characteristics of the patient. Some factors that may influence the customization of ACL reconstruction surgery include the patient's age, gender, activity level, preexisting knee conditions, and the severity of the ACL injury. The following are the examples according to the updated references:

1. Timing of surgery
2. Graft selection: The choice of graft material depends on various factors, including the patient's age, level of activity, and the surgeon's preference.
3. Deal with the concomitant injury
4. Surgical techniques: Single-bundle or double-bundle? Anterolateral augmentation or not?
5. Combined other procedures: Osteotomy

It is important to note that the standardization of the procedure can reproduce good surgery outcome, minimize the possibility of the mistakes and enhance the consistency and collaboration. Customization helps to ensure that the surgical procedure is tailored to the specific needs of each patient, which can improve outcomes and reduce the risk of complications. Ultimately, the balance between standardization and customization will depend on the specific surgical procedure and the needs of the individual patient

Preoperative and postoperative rehabilitation and injection strategies for meniscus injuries

半月板術前術後復健以及相關注射治療策略

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meniscus injuries are common among athletes, and many require surgical intervention. as operation techniques advance rapidly, pre and post op rehabilitation consistently plays an important part in both functional recovery rate and pain control. Preoperative rehabilitation goals include pain-free ROM and reduce swelling. This will greatly decrease postoperative pain and accelerate return to play timing.

postoperative rehabilitation goals include different phases of training, with gradual progression of isometric to isotonic training, and utilize the difference of open kinetic chain and close kinetic chain exercises. The final stages of rehab before return to play include sport specific drills include plyometrics, balance, agility, and eccentric contraction of lower limb contractile tissues. Checklists for each stage will mark the target of improvement and rate of progression, only when the requirements were fulfilled should the patient be allowed to keep progressing.

nonoperative patients should consider PRP injection, 50% of patients will benefit from the PRP with 40 to 60 percent improvement in clinical symptoms in one month. risk factors for nonresponsive PRP injections include multiple structural injuries, poor cooperation to designated exercises, and old age. most patients don’t require more than 3 injections.

Injection to meniscus can be done by ultrasound guidance, the most common approach to medial meniscus include the medial approach which either bypasses the MCL anteriorly or penetrates the MCL, and posterior approach which is more suitable for posterior horn tears. injections to lateral meniscus is less often practiced but can be done via similar fashion.

postoperative pain control can also be enhanced with ultrasound guided nerve blocks. Common nerves related to knee pain include infrapatellar branch of saphenous nerve, and geniculate nerves surrounding the knee joint. other related nerves include the Tibial and peroneal nerves, and also the posterior division of obturator nerve. nonetheless good adherence to rehabilitation protocols remain the foundation of postoperative knee pain control, and functional improvement.

Using biphasic osteochondral constructs for treating elbow osteochondritis dissecans(OCD) in adolescent

使用雙相骨軟骨結構治療兒童肘部剝脫性骨軟骨炎 (OCD)

Kuei-Hsiang Hsu, Jing-Pei La, Wen-Chieh Chang, Chi-Kuang Feng, Yu-Ping Su

許逵翔 賴璟霈 張文杰 奉季光 蘇宇平

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Background: The case report aims to present the results of the use of minced autologous cartilage implant (MACI) and biphasic osteochondral constructs for the treatment of severe elbow osteochondritis dissecans (OCD) in adolescent.

Methods: The study included two patients with grade 4 elbow OCD aged 13 and 14 years. The lesion was exposed through a posterior median approach. The whole displaced cartilage flap was collected and minced with a scalpel, followed by enzymatic digestion for 20 min. The processed cartilage fragments are then injected into the biphasic osteochondral scaffold. A hole the size of the scaffold was drilled in the subchondral bone below the OCD. Press the biphasic stent into the pre-drilled hole to replace the OCD lesion. Outcome measures included range of motion, Mayo Elbow Performance Score (MEPS), visual analog scale (VAS) for pain from 0-10, X-ray and MRI features, and perioperative complications.

Results: The follow-up duration was 12 and 15 months for two patients. No complications developed at last follow-up. For patient 1 and patient 2, the flexion-extension improved from 120-30 to 130-10 and 110-20 to 135-0 degree; supination-pronation improved from 50 to 85 and 60 to 90 degree; MEPS improved from 65 to 95 and 50 to 95; VAS improved from 9 to 1 and 8 to 1; X-ray and MRI demonstrated decreased OCD lesion size with satisfactory regenerated tissue filling at defect for both patients.

Conclusion: MACI with biphasic osteochondral composite is a safe and effective treatment option for elbow OCD.

Microfracture augmentation with Chitosan hydrogel with or without Bone Marrow Concentrate for Focal Articular Cartilage defect of knee: A preliminary clinical and radiological result

骨髓刺激合併 Chitosan hydrogel 治療膝關節軟骨缺損：臨床和影像學結果

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The purpose of the study is to compare microfracture augmentation with Chitosan hydrogel (JointRep®, Oligo Medic Inc. Quebec, Canada) with or without autologous Bone Marrow Concentrate (BMC) when treating symptomatic focal articular cartilage lesions in the knee joint at femoral condyles, trochlea or patellar. The outcomes are evaluated by clinical functional evaluation forms including Lysholm socre, VAS score and KOOS score. Radiological results were evaluated with preoperative and postoperative MRI.

Microfracture surgery represents a traditional reparative strategy based on bone marrow stimulation (BMS). This arthroscopic technique attempts to achieve cartilage regeneration by exposing, through perforations, chondral lesions to mesenchymal stem cells migrating from the bone marrow. This approach is inexpensive and relatively non-invasive but unfortunately leads to formation of fibrocartilage rather than hyaline cartilage; this new tissue is usually more dense with less stiffness when compared with the normal hyaline cartilage.

Chitosan hydrogel is a second generation chitosan-based bioscaffold content with Polyglucosamine/ glucosamine carbonate (PG/GC) and presenting of the property of Thermogelling injectable hydrogel, at body temperature 37℃ it will be solidified within one minute. Chitosan hydrogel applied over the microfracture defect surface and mixed with the blood clot from bone marrow, filled the chondral defect and enhanced the chondrogenesis.

Bone marrow concentrate (BMC) also serves as a rich source of factors that can influence the healing responses by decrease in cell apoptosis and inflammation, and by activation of cell proliferation, differentiation, and angiogenesis via paracrine and autocrine pathways.

Microfracture plus Chitosan hydrogel with bone marrow concentrate: aspiration of bone marrow blood 10cc from iliac creast, then centrifugation 20 minutes, then aspiration lowest 1 cc most concentrate bone marrow stem cell or nuclare cell, mixed it with Chitosan Hydrogel, then injected the hydrogel into the chondral defect site.

Between Jan 2022 and April 2023, total 62 patients received microfracture augmentation with Chitosan hydrogel in 50 patients and combination with BMC in 12 patients for focal articular cartilage defect of knee joint. Most of the patients (>90%) presented high satisfactory rate with significant improvement of knee function scores and MRI showed the defect was filled with the new chondral tissue.

Retrograde bone marrow stimulation for osteochondral lesion of talus

反向骨髓刺激治療距骨骨軟骨損傷

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Background: Symptomatic osteochondral lesions of the talus (OLT) is a common cause of ankle pain and frequently occur among recreational and professional athletes. The treatment principle in small sized OLT is bone marrow stimulation. In traditional, talar bone cartilages damage was unavoidable during this procedure. The purpose of current study was to introduce the retrograde bone marrow stimulation under arthroscopy specified for medial dome OLT with intact cartiladge.

Methods: To determine the effectiveness of retrograde arthroscopic bone marrow stimulation, 37 patients with medial talar dome OLT with intact cartiledge were included. Arthroscopic examination of ankle joint was first performed. After lesion localization arthroscopically, a retrograde bone tunnel was made from lateral talus aiming to the lesion. Then, multiple drilling and debridement was done through the tunnel under C-arm radiograph. After that, artificial bone substitute re-filling of the lesion was done.

Results: After a mean follow-up of 47 months, none of our patients suffered from major complication as uncontrollable infection, end-staged osteoarthritis that need surgical intervention, and progressed OLT lesion that needed osteochondral transplantation. The averaged American Orthopaedic Foot and Ankle Society (AOFAS) ankle and hindfoot score improved from 64.8 to 84.5.

Conclusion: We demonstrate that retrograde bone marrow stimulation under arthroscopy was a reliable minimal invasive procedure in certain circumstance. Future studies include the comparison of therapeutic effect between different infillings after debride of the lesion and re-classification of OLT in order to clarify the indication of this procedure and are needed.

InSpace subacromial balloon spacer for irreparable rotator cuff tear

InSpace 填充式水球治療不可修復的旋轉肌腱斷裂

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Background: Irreparable rotator cuff tears is still a challenging condition. Subacromial spacer to treat irreparable rotator cuff tears remain a controversial option in different consideration. With its benefit of low complication rate and easily procedure, we try to find out the most beneficial scenario and the suitable cases.

Methods: A retrospective cohort study of 22 cases who received subacromial spacer for irreparable rotator cuff tears pathology from 2019 Mar. to 2022 Jan. were enrolled in this study. The demographic data, radiographic image and functional outcome (ASES and constant score) were assessed and analyzed after operation 1, 3, 6, 9 and 12 month. Radiographic data was collected and MRI on 1 year after operation.

Results: Range of motion, ASES, constant score and VAS were improved significant at 12 months follow up. Acromiohumeral distance preserved without significant change after 12 months and it is not correlated to clinical outcome. The trend of VAS decrease significant in the first month after operation. ROM improves significant during 1-3 months. All patients were followed at least 12 months.

Conclusion: Subacromial spacer is an effective option to treat irreparable rotator cuff tears without pseudoparalysis. It provides immediately full range of motion and fast recovery after surgical procedure.

Bone health optimization in patients with PMO receiving hip surgery with anabolic agent

骨質優化評估應用至接受髖部手術與造骨促進劑之停經後病患

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Osteoporosis is associated with adverse orthopedic surgical outcomes. Bone health optimization (BHO) is a preoperative intervention intended to reduce the likelihood of postoperative complications. Optimization of medical conditions before orthopedic surgery is increasingly being performed to maximize outcomes, reduce the risk of adverse events, and improve efficiency.

Bone health optimization is a comprehensive program aimed at improving BMD, correcting modifiable factors related to bone health, and stimulating osteoblastic activity in the skeleton to condition the spine to optimize recovery after surgery. Several proposed guidelines for primary osteoporosis treatment and secondary fracture prevention can be adopted to identify patients who should have bone density measurement and laboratory testing and, when indicated, receive medical treatment before undergoing surgery. Poor bone health is common in elective surgery patients and that many meet criteria for medical therapy.

Additionally, preoperative bone assessment may affect surgical decision-making. In a survey of 465 joint arthroplasty surgeons, 77% indicated that bone quality influenced their choice of implant, but only 5% assessed bone density before the surgical procedure. A similar survey among spine surgeons showed that only 20% evaluated bone quality before revision surgery despite many reporting that osteoporosis may alter surgical technique. Clearly, the importance of identifying poor bone health before a surgical procedure is well known, but it is poorly implemented. Therefore, it is important to characterize a patient population referred for bone health optimization prior to elective surgery.

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神經疾病的精準診斷及治療

Cutting-Edge Precision Diagnosis and Treatment in Neurology

時 間：112年7月9日 08:20~12:00

Time：July 9, 2023 08:20~12:00

地 點：臺北榮民總醫院 致德樓第三會議室

Place：The Third Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

神經疾病的精準診斷及治療

Cutting-Edge Precision Diagnosis and Treatment in Neurology

Evolving paradigms in ALS therapy development

ALS 治療的最新發展

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The US Food & Drug Administration (FDA) has approved 4 drugs for the treatment of ALS – riluzole, edaravone, sodium phenylbutyrate/TUDCA and tofersen. Dozens of other drugs are in (or being readied for testing in) clinical trials. It is timely, therefore, to reflect on traditional approaches to ALS therapy development, and the value in changing these paradigms based on an evolving understanding of ALS. This talk will consider four such paradigms: (1) The shift from broad eligibility criteria to the use of enrichment criteria to enroll a more homogeneous patient population with faster progressing disease likely contributed to the success of recent trials. It is surprising, therefore, that trials are now reverting to broader eligibility criteria. (2) Biomarkers are widely recognized as valuable drug development tools, but their effective use requires a nuanced understanding of their context-of-use. (3) Traditionally, outcome measures in Phase-3 ALS trials have relied on changes in the ALS functional rating scale-revised, tracheostomy-free survival, or a combination of the two. Phase-2 studies have relied on the same measures but are typically underpowered. Lessons from the trial of tofersen in SOD1-ALS offer important insights into the potential role for biomarkers as outcome measures, most notably neurofilament light chain. (4) The efficacy of a therapeutic agent is likely to be greatest if treatment is initiated early. The study of pre-symptomatic gene mutation carriers at markedly elevated risk for ALS has empowered initiation of the first-ever ALS prevention trial for people at risk for SOD1 ALS, but with implications for early diagnosis and treatment of patients with non-genetic ALS.

Research targets for dementia therapy

失智症治療的研究目標

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The diagnosis of Alzheimer's disease is in the middle of a transition from a diagnosis of exclusion to a diagnosis of inclusion. This biomarker specific approach increases accuracy from 66-75% to over 90%. The use of disease specific biomarkers comes from the recasting of AD from the clinical phenotype to the pathological definition using the A/T/N criteria. The use of biomarkers increases precision in diagnosis but will need to be used to select and identify patients suitable for the new disease modifying treatments in the form of the anti-Ab monoclonal antibodies (aducanumab, lecanemab, donanemab). The presentation will review PET, CSF and plasma diagnostics and well as the emerging treatments for AD.

Recent advances in migraine treatment

偏頭痛治療的最新進展

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Migraine is one of the most prevalent neurological disorders, and has been the second leading cause of disease burden around the world. One of the most important advances in the understanding of migraine pathophysiology is the release of calcitonin gene-related peptide (CGRP) during migraine attacks, which is the target of many of novel treatment agents.

Migraine treatment constitutes acute and preventive treatment. Acute medications are meant to provide rapid symptom relief. Triptans are 5-$HT_{1B/1D}$ agonists that could reduce the release of CGRP, and thereby terminate acute migraine attacks. However, even though they are categorized as migraine-specific medications, there are still potential concerns about vasoconstriction and increased vascular risks due to activation of the 5-HT_{1B} receptors. In recent years, two classes of new drugs were developed to address such concerns, namely ditans and gepants, which are 5-HT_{1F} agonists and CGRP receptor antagonists, respectively. Their efficacies and tolerabilities were demonstrated by the pivotal trials. Currently, lasmiditan, rimegepant, and ubrogepant were approved.

For patients with higher attack frequencies, greater disabilities, or failure or contraindications for acute treatment, preventive treatment could be considered. Traditional oral preventive medications are useful in reducing headache frequency, although their use could be limited by intolerable side effects since these drug were not specific. OnabotulinumtoxinA was shown to be effective in the preventive treatment of chronic migraine, namely headache occurring on ≥15 days a month, 8 of which are migraine days, for > 3 months. The mechanism of action was believed to be reduction in CGRP release. Later on, four monoclonal antibodies have become approved in the preventive treatment of episodic and chronic migraine. One of which targets the CGRP receptor, i.e., erenumab, and the other three target the CGRP molecule, i.e., galcanezumab, fremanezumab, and eptinezumab. These injectables are relatively devoid of systemic side effects, and are therefore much better tolerated. The availability of these newly available mechanism-based agents has revolutionized the treatment for patients with migraine.

Effects of bihemispheric transcranial direct current stimulation on motor recovery in subacute stroke patients

雙腦經顱直流電刺激對亞急性中風病人動作恢復之效應

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I will review current understanding of post-acute stroke recovery, and present our work to improve such recovery utilizing transcranial direct current stimulation (tDCS) in subacute stroke patients. Bihemispheric tDCS of the primary motor cortex (M1) can simultaneously modulate bilateral corticospinal excitability and interhemispheric interaction. However, how tDCS affects subacute stroke recovery remains unclear. We enrolled subacute inpatients who had first-ever stroke at subcortical regions and moderate- to-severe baseline Fugl-Meyer Assessment of Upper Extremity (FMA-UE) score 2–56. Participants between 14 and 28 days after stroke were double-blind, randomly assigned (1:1) to receive real or sham tDCS (with ipsilesional M1 anode and contralesional M1 cathode, 20 min, 2 mA) during task practice twice daily for 20 sessions in two weeks. Residual integrity of the ipsilesional corticospinal tract was stratified between groups. The primary efficacy outcome was the change in FMA-UE score from baseline (responder as an increase ≥ 10). The secondary measures included changes in the FMA-Lower Extremity (FMA-LE) and explorative resting-state MRI functional connectivity (FC) of target regions after intervention and three months post-stroke. Thirty-eight participants completed the study without significant adverse effects. The majority had no recordable baseline motor-evoked potentials (MEP-negative) from the paretic forearm. Compared with the sham group, the real tDCS group showed enhanced improvement of FMA-UE after intervention, which sustained three months post-stroke. Interestingly, in the MEP-negative subgroup analysis, the FMA-UE improvement remained but delayed. Additionally, the FMA-LE improvement after real tDCS was not significantly greater until three months post-stroke. We found that the individual FMA-UE improvements after real tDCS were associated with bilateral intrahemispheric, rather than interhemispheric, FC strengths in the targeted cortices, while the improvements after sham tDCS were associated with predominantly ipsilesional FC changes after adjustment for age and sex. In summary, bihemispheric tDCS during task-oriented training may facilitate motor recovery in subacute stroke patients, even with compromised corticospinal tract integrity. Further studies are warranted for tDCS responder prediction and network-specific neuromodulation.

Focused ultrasound in the treatment for drug resistant epilepsy

聚焦超音波於頑性癲癇治療之應用

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Epilepsy is a chronic neurological disorder and 70% of people with epilepsy (PWE) whose seizures could be well controlled by antiseizure medication. For the remaining 30% of PWE, defined as drug-resistant epilepsy (DRE), surgical treatment and other alternatives are options. Seizure freedom could be achieved in 60-80% of surgically-remediable DRE patients. For patients who are not suitable for resective surgery, neuromodulation is a consideration. The present approved neruomodulation for epilepsy (VNS, DBS, and RNS) need device implantation and it increased the risk of device related adverse effect, for example, bleeding, infection and device break issue. Transcranial focused ultrasound (tFUS) is an emerging treatment for various neurological disorders and has been proven for the treatment of essential tremor and Parkinson's disease by its lesional effect. It is incision-less which is less invasive compared to previous neuromodulation modalities. tFUS has the potential to be a new solution for DRE. The preclinical data showed that the seizure activities were reduced by tFUS in acute and chronic epilepsy animal models. Several recent reports in human had demonstrated that seizure frequency reduced after lesioning the key target by tFUS. In addition, it also showed optimistic results in controlling seizures by using its neuromodulation effect in people with epilepsy. Our phase 1 study has showed the feasibility and safety of tFUS in DRE through a neuromodulation effect. The intracranial EEG also showed alteration after sonication at the seizure onset targets. A phase 2 study is now ongoing, and I will share the preliminary data and the perspective of the future clinical tFUS use in epilepsy.

MRgFUS(transcranial Magnetic Resonance guided Focused Ultrasound) therapy for movement disorder, single center experience

磁振導航聚焦超音波治療目前在動作障礙疾病上之應用

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The MRgFUS (transcranial Magnetic Resonance guided Focused Ultrasound) is a new technology of stereotactic neurosurgery which is minimal invasive. It was applicated in treating essential tremor first since 2014, and then it is applied to treat Parkinson's disease, focal hand dystonia, and even in chorea in some cases.

In 2017, the Changbin Show Chwan Memorial Hospital, we had set the first MRgFUS machine in Taiwan. We also invited Professor Taira Takaomi to share his clinical experiences and technics of the VIM thalamotmy for essential tremor and the PTT tractomy for Parkinson disease and dystonia to us.

We had performed the VIM(ventralis intermediate nucleus) thalamotomy for essential tremor for around 150 cases since 2017 and PTT(pallido-thalamic tract) tractomy for Parkinson's disease for around 30 patients. The clinical experiences was published in 2021 as the title" Focused Ultrasound Thalamotomy for the Treatment of Essential Tremor: A 2-Year Outcome Study of Chinese People". The post operation data was similar with other published data for VIM thalamotomy, and we even had the lower complication rate compared to other published data.

Today, I would like to introduce the whole basic principles and manuals of MRgFUS, and I would share our targeting experience of MRgFUS.

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腎臟移植之尖端醫療新紀元

Kidney Transplantation: A New Era of Cutting - Edge Medical Care

時 間：112年7月9日 08:20~12:00

Time：July 9, 2023 08:20~12:00

地 點：臺北榮民總醫院 致德樓第四會議室

Place：The Fourth Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

腎臟移植之尖端醫療新紀元

Kidney Transplantation: A New Era of Cutting - Edge Medical Care

Application of robotic surgery in kidney transplantation

達文西手術於腎臟移植之運用

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The utilization of the minimally invasive approach is a major innovation in transplant surgery. More recently, robotic-assisted techniques have allowed for increased visual field perception, essential for performing deep anastomosis in the pelvis and ergonomic control with three-dimensional navigation. The major advantage of this minimally invasive approach is to minimize the incidence of wound complications in high risk population, such as the obese patients. The first robotic approach to kidney transplant was described by Hoznek in 2001. Thereafter, a variety of unique approaches were developed within the decade with the aim to reduce the morbidity of kidney transplant in these obese patients. My presentation will focus on the application of robotic surgery in kidney transplantation based on the personal experience, and the outcomes based the evidence-based literature review.

Retroperitoneal laparoscopic living kidney donation and renal vein reconstruction

後腹腔鏡活體腎臟捐贈手術與腎靜脈重建

Cheng-Yen Chen

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Background: Compared to laparoscopic transperitoneal (LTP) and retroperitoneal (LRP) living donor nephrectomy, the retroperitoneal approach has some dominant advantages, such as less postoperative ileus and nearly no risk of abdominal adhesions. However, it needs a higher learning curve to overcome the disorientation in the retroperitoneal space, especially for the general surgeon instead of the urologist.

Methods: Since Nov. 2014, we have changed our program of living donor nephrectomy from open or laparoscopic transperitoneal to retroperitoneal approach and enrolled 115 LRPs until August 2022. Of the 115 LRP cases, 20 donors donated their kidneys. In addition, we harvested a segmental right gonadal vein in the same operative field to lengthen the right renal vein.

Results: All 115 cases completed the retroperitoneal nephrectomy without conversion to open or transperitoneal methods. Compared to our previous open and LTP cases, the LRP donors had less intraoperative bleeding (Open/LTP/LRP, mean, ml: 165.8/68.5/54.4, $p < 0.001$) and earlier oral intake (Open/LTP/LRP, mean, day: 1.4/1.8/1.3, $p = 0.039$), but longer operation time (Open/LTP/LRP, mean, min: 267.2/290.8/348.9, $p < 0.001$). For the right kidneys, we The renal vein could extend 1.5-2cm in length after venoplasty.

Conclusion: From our experience, the LRP nephrectomy is replicable, even for the beginner, without exploring retroperitoneal space. Although the initial cases would spend more operation time, the donor's recovery is better than the open or LTP approach.

Immunogenicity safety and outcomes of SARS-CoV-2 vaccination in kidney transplant recipients

新冠肺炎疫情下之腎臟移植病患觀察：疫苗保護力、感染率及預後

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Kidney transplant patients exhibit a poor response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination. We prospectively analyzed both anti-spike protein antibody and cellular responses 1 month after the first and second doses of SARS-CoV-2 vaccines in 171 kidney transplant patients after vaccination with four different vaccines, including one viral vector (ChAdOx1 nCov-19, n = 30), two mRNA (mRNA1273, n = 81 and BNT162b2, n = 38), and one protein subunit (MVC-COV1901, n = 22). Among the four vaccines, mRNA1273 elicited the strongest humoral response and induced the highest interferon-γ levels in patients with a positive cellular response to the spike protein. A transient elevation in creatinine levels was noted in approximately half of the patients after the first dose of mRNA1273 or ChAdOx1.

We also retrospectively analyzed the risk of SARS-CoV-2 infection in a single medical center according to vaccine doses and immune responses prior to the outbreak to evaluate the vaccine's real-world effectiveness. Among 622 kidney transplant patients, there were 77 patients without vaccination, 26 with one dose, 74 with two doses, 357 with three, and 88 with four doses. Patients who received more than three vaccinations had a lower risk of infection (odds ratio=0.6527, 95%CI=0.4324-0.9937) and hospitalization (odds ratio=0.3161, 95%CI=0.1311-0.7464). Antibody and cellular responses were measured in 181 patients after vaccination. An anti-spike protein antibody titer of more than 1642 BAU/mL is protective against SARS-CoV-2 infection (odds ratio=0.4136, 95%CI=0.1800-0.9043). A cellular response by interferon-γ release assay was not correlated with the disease (odds ratio=1.001, 95%CI=0.9995-1.002). Multiple doses of vaccine and high antibody titers provided better protection against the Omicron variant in kidney transplant recipients.

Ethics in organ transplant and the current allocation system in Taiwan

器官移植倫理與目前臺灣的分配制度

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From the perspective of the four major principles of medical ethics, let's explore common ethical issues related to organ donation and transplantation:

1. Ethical Issues in Cadaveric Organ Donation and Transplantation
2. Ethical Issues in Living Organ Donation and Transplantation
3. Ethical Issues in Designated Donation
4. Ethical Issues of Organ Donation after Cardiac Death (DCD)
5. Ethical Issues of Living Donor Kidney Paired Exchange Donation Transplantation
6. Common ethical conflicts and ways of dealing with them

The current allocation system in Taiwan:

1. History, Origins, and Current Situation of Organ Donation and Transplantation in Taiwan
2. Introduction and tasks of the Organ Donation and Transplant Registration Center
3. Introduction to Organ Procurement Organization (OPO) Program (including Eye Bank and Tissue Preservation Bank)
4. Introduction to organ solicitation systems in various countries
5. Introduction to the Registration System for Organ Donation and Transplantation
6. organ donation promotion and organ donation consent signing on the National Health Insurance (NHI) card
7. Challenges and Dilemmas Faced in Organ Donation
8. The Promotion and Vision of Organ Donation

Treatment of antibody-mediated rejection in kidney transplantation: Taipei Veterans General Hospital's experience

腎臟移植抗體性排斥之治療：臺北榮總之經驗

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Kidney transplantation is considered as the optimal form of renal replacement therapy. Efficient immunosuppression regimens have helped to achieve long graft survival, but medication non-adherence and rejections remain a significant threat to graft survival. Among rejections, antibody-mediated rejection (AMR) has been recognized as the leading cause of kidney graft failure in recent years.

The therapy for acute AMR is usually aimed to rapidly lowering the circulating DSA with either plasmapheresis or immunoadsorption, and modulating their activity with intravenous immunoglobulins (IVIG). Additional therapy commonly consists of methylprednisolone and optimized the basal immunosuppression. Other treatments include targeting T cells with thymoglobulin, B cells with rituximab and plasma cells with bortezomib. The experience of evaluation and treatments in antibody mediated rejection in the past days at VGH-Taipei will be presented.

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後疫情時代皮膚的免疫調適

Post COVID-19 Immune Adaptation in Skin

時 間：112年7月9日 08:50~12:00

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Place：The Conference Room 6&7, Chih-Teh Building
Taipei Veterans General Hospital

後疫情時代皮膚的免疫調適
Post COVID-19 Immune Adaptation in Skin

Chronic spontaneous urticaria treatment with omalizumab in post pandemic era

後疫情時代使用 omalizumab 治療慢性自發性蕁麻疹

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臺北榮民總醫院 內科部 過敏免疫風濕科

Urticaria – also known as hives, weals, welts or nettle rash – is a raised, itchy rash that appears on the skin. It may appear on one part of the body or be spread across large areas. The rash is usually very itchy and ranges in size from a few milli meters to the size of a hand. Although the affected area may change in appearance within 24 hours, the rash usually settles within a few days. Symptoms lasts longer than 6 weeks could be defined as chronic. 1/3 of chronic urticaria patients are CIU (chronic inducible urticaria) and 2/3 of chronic urticaria patients are CSU (chronic spontaneous urticaria).

Omalizumab has been approved for the treatment of CSU by the European Medical Agency (300 mg every 4 weeks) and by the U.S. Food and Drug Administration (150-300 mg every4weeks). Omalizumab has also been approved for the treatment of CSU by Taiwan Food and Drug Administration (150-300 mg every4weeks). The efficacy of Omalizumab in treatment of CSU can provide a significant improvement in CSU activity and quality of life, and is well tolerated. Also, The recent EAACI/GA2 LEN/EDF/WAO guidelines recommend omalizumab (anti-IgE) for the management of patients aged ≥12 years with chronic urticaria unresponsive to high-doses second-generation H1 -antihistamines (anti-H1).

In this lecture, we would like to address the importance of Omalizumab in CSU treatment with or without the presence of COVID-19 pandemic, comparing the efficacy data in in different groups, across gender, age, ethnicity, etc. With the aim to understand how CSU patients and subgroups might be affected by the COVID-19 pandemic in their disease activity and control and whether the treatment adjustment during/ post pandemic is required.

Challenges of managing atopic dermatitis during the COVID-19 pandemic

新冠肺炎肆虐下異位性皮膚炎控制之挑戰

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Atopic dermatitis (AD) is a common, chronic inflammatory skin disease associated with itch, pain, sleep disturbance, anxiety, depression, and increased health care utilization. AD can also have a significantly negative impact on quality of life (QoL). It is multifactorial, with genetic predisposition and environmental factors both known to contribute to onset of the condition.

There is an incomplete understanding of the relationship between AD and the risk of COVID-19 infection. Data concerning COVID-19 infection rates in AD patients are inconsistent, with some studies finding an increased incidence of infection and others showing no significant difference. The impact of the COVID-19 pandemic on the AD population is also not well established. Reports have shown increased instances of skin irritation and disease because of prolonged use of personal protective equipment (PPE) and the chronic levels of stress that exacerbates AD. The extraordinary, persistent stress associated with coping with a chronic skin condition and the threat of catching COVID-19 also creates additional anxiety for patients. Preventive measures during the pandemic, such as social distancing have also changed patients' willingness to seek medical care because they do not want to burden the system with nonemergency situations during the pandemic. Patients also found it more challenging to get appointments and lacked trust in telephone consultations. There is also debate about whether to continue systemic immune-modulating treatment during the pandemic, because immunosuppression theoretically might increase the risk of COVID-19 infection or impede the immunogenicity of COVID-19 vaccine.

In this presentation we will discuss the challenges of managing AD in Taiwan during COVID-19 pandemic as well as a novel oral JAK1 inhibitor, abrocitinib, which is now approved by the TFDA for moderate to severe atopic dermatitis patients who are 12 years and older, which may be an effective treatment to be added to dermatologists' repertoire of advanced systemics.

Current treatment barrier and future perspective in PsO and PsA

乾癬及乾癬性關節炎的當前治療障礙和未來前景

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Psoriasis (PsO) is a systemic inflammatory disease with prominent skin manifestations, about 30% of them develop psoriatic arthritis (PsA). Patients with PsO and concomitant PsA had greater degrees of skin and nail involvement and experienced greater negative impacts on QoL. Disease interception suggests that early intervention in patients with PsO may prevent progression to PsA. The need for a diagnosis and definition of 'early' or 'pre-PsA' should be pursued, and treatment trials designed with the goal of early disease eradication or prevention. It is important to consider treatment options with good efficacy in both skin and joint that last long.

At the end of this speech, participants should be able to:

- Understand the pathophysiology of psoriasis and potential to progress to PsA
- Differentiate biologic therapies based on mechanisms, indication, efficacy and safety data, and impact on patient-reported outcomes etc.
- Integrate insights from real-world and clinical evidence on psoriasis and PsA into clinical practice.
- The role of IL-23 in treatment of PsO and PsA.
- Discuss the role of advanced treatment optimization strategies in achieving and maintaining disease freedom in patients with psoriatic disease.

Hair loss after COVID-19: Why it happens and how to stop

疫情後的落髮：他是怎麼發生的？能如何治療？

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The list of possible COVID-19 side effects is as lengthy and diverse as the list of potential symptoms. Among those possible lingering issues is hair loss after COVID-19, a troubling side effect that emerged early on in the pandemic, leaving many people confused and concerned.

Even though many things about COVID-19 are still shrouded in mystery, our understanding of the illness that completely changed life as we know it is growing, postvirus hair loss included.

According to dermatologists and an evolving body of scientific research, we now not only know that hair loss after COVID-19 is, in fact, a very real thing, but we're continuing to learn more and more about the mechanisms behind it. The good news is that, for most people, hair loss after COVID-19 is not permanent.

Here, dermatologists explain the connection between COVID-19 and hair loss—and what you can do if you're experiencing this unique type of shedding.

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第2型糖尿病人使用 Metformin 之臨床效果

Metformin Use and Clinical Outcomes Among Patients with Type 2 Diabetes

時 間：112年7月9日 08:20~12:00

Time：July 9, 2023 08:20~12:00

地 點：臺北榮民總醫院 致德樓第八、九會議室

Place：The Conference Room 8&9, Chih-Teh Building
Taipei Veterans General Hospital

第2型糖尿病人使用 Metformin 之臨床效果

Metformin Use and Clinical Outcomes Among Patients with Type 2 Diabetes

Metformin: From basic to clinical

Metformin: 從基礎到臨床

Yao-Hsien Tseng

曾耀賢

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臺中童綜合醫院 內分泌新陳代謝科

Metformin (dimethylbiguanide) is among the most widely used anti-diabetic drugs. Metformin's history is linked to Galega officinalis (also known as goat's rue), a traditional herbal medicine in Europe, found to be rich in guanidine, which, in 1918, was shown to lower blood glucose. French physician Jean Sterne, who first reported the use of metformin to treat diabetes in 1957. The ability of metformin to counter insulin resistance and address adult-onset hyperglycemia without weight gain or increased risk of hypoglycemia gradually gathered credence in Europe, and after intensive scrutiny metformin was introduced into the USA in 1995. Long-term cardiovascular benefits of metformin were identified by the UK Prospective Diabetes Study (UKPDS) in 1998, providing a new rationale to adopt metformin as initial therapy to manage hyperglycemia in type 2 diabetes.

Metformin results in clear benefits in relation to glucose metabolism and diabetes-related complications. The mechanisms underlying these benefits are complex and still not fully understood. Studies over the past few years have identified multiple novel molecular targets and pathways that metformin acts on to exert its beneficial effects in treating type 2 diabetes as well as other disorders involving dysregulated inflammation and redox homeostasis. Physiologically, metformin has been shown to reduce hepatic glucose production, yet not all of its effects can be explained by this mechanism and there is increasing evidence of a key role for the gut. Metformin has been shown to act via both AMP activated protein kinase (AMPK)-dependent and AMPK independent mechanisms; by inhibition of mitochondrial respiration but also perhaps by inhibition of mitochondrial glycerophosphate dehydrogenase, and a mechanism involving the lysosome. Identification of these novel targets and pathways not only deepens our understanding of the molecular mechanisms by which metformin exerts diverse beneficial biological effects, but also provides opportunities for developing new mechanistically based drugs for human diseases. Research discoveries on novel molecular targets of metformin in glycemic control, cardiovascular protection, cancer intervention, anti-inflammation, anti-aging, and weight control. Sixty-five years after its introduction in diabetes treatment, metformin has become the most prescribed glucose-lowering medicine worldwide with the potential for further therapeutic applications.

Emerging complications of diabetes

糖尿病新興併發症

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Type 2 diabetes is a metabolic, chronic disorder characterized by insulin resistance and elevated blood glucose levels. In recent decades, large increases in diabetes prevalence have been demonstrated in virtually all regions of the world. The traditional complications of diabetes mellitus are well known and continue to pose a considerable burden on millions of people living with diabetes mellitus. Although a large drug portfolio exists to keep the blood glucose levels under control, these medications are not without side effects. More importantly, once diagnosed diabetes is rarely reversible. Dysfunctions in the kidney, retina, cardiovascular system, neurons, and liver represent the common complications of diabetes, which again lack effective therapies that can reverse organ injury.

Advances in the management of diabetes mellitus and, consequently, longer life expectancies, have resulted in the emergence of evidence of the existence of a different set of lesser-acknowledged diabetes mellitus complications. With declining mortality from vascular disease, which once accounted for more than 50% of deaths amongst people with diabetes mellitus, cancer and dementia now comprise the leading causes of death in people with diabetes mellitus in some countries or regions. Additionally, studies have demonstrated notable links between diabetes mellitus and a broad range of comorbidities, including cognitive decline, functional disability, affective disorders, obstructive sleep apnea and liver disease, and have refined our understanding of the association between diabetes mellitus and infection. There is a need to increase the awareness of emerging complications among primary care physicians at the frontline of diabetes mellitus care, and a place for screening for conditions such as depression, liver disease and cancers in diabetes mellitus guidelines should be considered. Given the growing burden of these emerging complications, the traditional management of diabetes mellitus might need to broaden its horizons.

Long-term benefits of metformin in patients with Type 2 Diabetes

Metformin 對第 2 型糖尿病人的長期益處

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Metformin is a synthetic derivative of guanidine, isolated from the extract of Galega officinalis. The UK Prospective Diabetes Study (1998) demonstrated that metformin could significantly reduce cardiovascular events in patients with Type 2 Diabetes mellitus (T2D). Metformin has been used worldwide since 1998, and it is by far the first-line anti-diabetic drug for the management of T2D. It can reduce blood sugar and modulate metabolism by inhibiting mitochondrial respiratory-chain complex-1 and activating the adenosine monophosphate (AMP)-activated protein kinase (AMPK). Also, there's many novel target for metformin had been reported. Therefore, metformin has demonstrated diverse beneficial effects apart from glucose-lowering effect.

There have been reports indicating that metformin may have a beneficial effect on infections such as tuberculosis, influenza, and sepsis. Studies conducted using the Taiwan National Health Insurance (NHI) Research Database have also shown similar results, suggesting that metformin use may lower the risk of herpes zoster and bacterial pneumonia. While metformin did not show a significant difference in the risk of urinary tract infections (UTI), another study found that it was associated with a lower risk of UTI-related mortality. Metformin has also been associated with lower all-cause mortality and cardiovascular disease in patients with T2D and chronic obstructive pulmonary disease. Another study showed a lower risk of influenza and its complications when metformin was used prior to influenza vaccination. From the above, we could conclude that metformin has many effects beyond its ability to lower blood sugar levels. Long-term use of metformin not only improves complications caused by hyperglycemia, but also provides numerous other benefits.

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探索最新淋巴水腫診斷及治療方式

Explore Current Diagnosis and Treatment of Lymphedema

時　間：112年7月9日　09:00~12:00

Time：July 9, 2023　09:00~12:00

地　點：臺北榮民總醫院 中正樓3樓 外科部會議室

Place：3F, The Conference Room, Chih-Teh Building
Taipei Veterans General Hospital

探索最新淋巴水腫診斷及治療方式

Explore Current Diagnosis and Treatment of Lymphedema

Next level of imaging techniques for lymphatic supermicrosurgery

運用高階影像技術於淋巴超顯微手術

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Preoperative and intraoperative detection and selection of the lymphatic vessels are important for maximizing therapeutic efficacy of lymphedema supermicrosurgery. As technology advances, high definition imaging tools could become progressively more powerful in diagnostic procedure and surgery. I present capability of ultra high-frequency ultrasound and laser tomography for imaging of the lymphatic vessels for surgery of lymphedema, which may overcome the weakness of the conventional imaging techniques.

These imaging tool provides real-time images of the lymphatic vessels in extremely high resolution and enables evaluation of lymphatic lumen condition pre/intra-operatively and objective post-LVA anastomosis status intraoperatively. The advanced technology for lymphedema supermicrosurgery may open new frontiers and have infinite possibilities.

How I do LVA: Lessons learned from 20,000+ anastomoses

如何作淋巴靜脈吻合：從超過二萬個淋巴靜脈吻合術所學到的經驗

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[Introduction] Supermicrosurgical lymphaticovenous anastomosis, or lymphaticovenular anastomosis (LVA) surgery is a least invasive surgical treatment of lymphedema. Since 2009, the presenter has performed over 20,000 anastomoses, and revised the surgical procures and perioperative management.

[Practice in 2009] LVAs were indicated for all lymphedema patients regardless of severity stage, and performed as many as possible during a given operation time regardless of lymphography findings; average #LVAs over 10. Side-to-end anastomosis was preferably performed regardless of vessels' conditions. Patients were hospitalized for at least 1 week, and compression was resumed 1 week after LVA.

[Current practice] LVA indication is considered based on thorough lymphedema evaluations including various imaging modalities of MRI, SPECT/CT, ICG lymphography (ICGL), and lymphatic ultrasound (LUS). LVAs are performed on selective sites where dynamic ICGL shows overlapping pattern and LUS localizes patent lymph vessels and suitable recipient veins; average #LVAs less than 5. Side-to-end anastomosis is performed only when a vein shows no reflux and a lymph vessel is less sclerotic; otherwise, end-to-end anastomosis is performed. Compression is resumed immediately after LVA surgery, and most patients undergo day surgery without hospitalization.

[Key evidence: why I change my practice] LVA efficacy is maximized, when pathophysiological severity is appropriate for LVA; ICG stage II-IV is best for LVA. Intact lymph vessel should not be used, rather slightly sclerotic ones should be used for LVA to salvage them; "s1" lymph vessels are best. Long-term patency of LVA is significantly affected by venous reflux, except for end-to-end anastomosis; side-to-end, end-to-side, or side-to-side anastomosis using a reflux vein would result in anastomosis site thrombosis. External compression makes only lymphatic pressure higher; continuous lymph-to-vein flow can be achieved to prevent anastomosis site thrombosis.

[Conclusion] It is crucial to understand what has been performed/abandoned previously, and all surgeons should keep improving their practice by objectively analyzing their previous practice's results with appropriate evaluations.

Systemic effects of gynecologic cancer-related lower limb lymphedema

婦癌相關之下肢淋巴水腫對於全身性的影響

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Gynecologic cancer-related lymphedema is localized in the lower extremities, it can be either unilateral or bilateral. The effects of lymphedema were once believed to be regional on the affected limbs, including tissue swelling, limited range of motion, cellulitis attacks, as well as fat deposition. However, based on our clinical experiences and basic research, the correlations between lower limb lymphedema, muscle edema in the contralateral and oxidative stress as well as dysregulated gene expression states otherwise.

Update on lymphedema management

淋巴水腫治療的新發展

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Lymphatic system has been considered as the third circulation system in human body. It is responsible for collecting and transporting excessive tissue fluid back to trunk and goes into venous system eventually. Once it is obstructed or damaged due to a variety of reasons such as surgery, radiotherapy, or severe infection, a swollen area distal to the obstructed area will become noticeable. For example, arm lymphedema would occur after axillary lymph node dissection. Leg lymphedema would occur after pelvic lymph node dissection.

The diagnosis could rely on history, physical examination, lymphoscintigraphy, or ICG lymphography. The management include non-surgical and surgical methods. The conventional non-surgical method is complete decongestive therapy (CDT), consisting of manual lymphatic drainage, compression, exercise, and skin care. Surgical management could be categorized into ablative, physiologic, or hybrid.

Lymphovenous anastomosis (LVA) is one of the most performed microsurgical procedures to treat lymphedema. A variety of related issues will be discussed in the presentation, such as how to avoid venous reflux, when to do LVA, where to do LVA, how effective is LVA, which configuration of LVA is better. How to prevent lymphedema by LVA will also be discussed.

In addition to addressing extremity lymphedema, head neck lymphedema, or lymphatics in the heart or brain will also be discussed in this presentation.

「醫學研究論文獎」及
「盧致德院長獎」論文摘要

「盧致德院長獎」
(從刊登於中華醫學會雜誌上的全部論文中，選出被引用
20 次以上的作者，並以其中最多次者頒發盧致德院長獎)

「醫學研究論文獎」及「盧致德院長獎」論文摘要

1 財團法人中華醫學研究獎助基金會
The effects of acupuncture and related techniques on patients with rheumatoid arthritis: A systematic review and meta-analysis ..... 臺北榮總 傳統醫學部 盧禾滻醫師 張清貿醫師

2 財團法人消化醫學研究發展基金會
Lycopene treatment improves intrahepatic fibrosis and attenuates pathological angiogenesis in biliary cirrhotic rats ..... 臺北榮總 胃腸肝膽科 黃惠君醫師 許劭榮醫師

3 財團法人兼善醫學基金會
Repeated loco-regional therapies for hepatocellular carcinoma is associated with inferior outcome after living donor liver transplantation in cirrhotic patients ..... 臺北榮總 移植外科 鄒奕帆醫師

4 財團法人心臟醫學研究發展基金會
Prolonged sitting time links to subclinical atherosclerosis ..... 臺北榮總 心臟內科 林淑馨醫師

5 財團法人泌尿外科醫學研究發展基金會
Effects of nerve-sparing procedures on surgical margins after robot-assisted radical prostatectomy ..... 振興醫院 泌尿科 楊景偉醫師

6 財團法人思源內科醫學研究發展基金會
Real-world effectiveness and safety of golimumab in rheumatoid arthritis treatment: A two-center study in Taiwan ..... 部立桃園醫院 過敏免疫風濕科 王淳峻醫師

7 財團法人吳舜文神經科學發展基金會
Risk factors of recurrent carotid blowout syndrome and strategy of endovascular management ..... 臺北榮總 放射線部 羅兆寶醫師

8 財團法人台灣癌症臨床研究發展基金會
Efficacy of cetuximab-containing regimens in the treatment of recurrent/metastatic head and neck cancer after progression to immune checkpoint inhibitors ..... 臺中榮總 血液腫瘤科 賴正倫醫師

9 財團法人李美蓉癌症醫學研究基金會
Clinical outcomes and metastatic behavior between de novo versus recurrent HER2-positive metastatic breast cancer: A 17-year single-institution cohort study at Taipei Veterans General Hospital ..... 臺北榮總 一般外科 鄭涵方醫師

10 財團法人中華醫學研究獎助基金會盧致德院長獎
Potential therapeutic agents against COVID-19: What we know so far ..... 臺北榮總 藥劑部 盧志嘉藥師

Journal of the Chinese Medical Association (2022) 85: 388-400

The effects of acupuncture and related techniques on patients with rheumatoid arthritis: A systematic review and meta-analysis

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Abstract

Background. One new type of acupuncture and related techniques (ACNRT) is increasingly used by rheumatoid arthritis (RA) patients to control their disease and improve their quality of life. However, the efficacy of using ACNRT in combination with western medicine (WM) for this purpose remains unknown.

Methods. Randomized controlled trials of ACNRT and WM treatments for RA from January 1, 2000, to January 31, 2021, were searched for in the databases PubMed, Embase, Medline, and the Cochrane Central Register of Controlled Trials, as well as in three Chinese databases: China National Knowledge Infrastructure, Wanfang Data, and Airiti Library. The primary outcomes consisted of inflammatory markers including C reactive protein (CRP), erythrocyte sedimentation rate (ESR), and rheumatoid factor. The secondary outcomes were clinical characteristics including pain visual analog scale (VAS) score, Disease Activity Score (DAS-28), swollen joints count (SJC), tender joints count (TJC), morning stiffness, and the results of a health assessment questionnaire. The three types of ACNRT used in the focal trials were acupuncture, moxibustion, and electro-acupuncture. Two qualified researchers extracted data from these trials' results and independently assessed their risk of bias. Statistical analyses were performed using Comprehensive Meta-Analysis V3 software.

Results. A total of 12 RCTs with 874 patients met the inclusion criteria. As compared with the patients who received WM treatment alone, those who were given integrated ACNRT/WM treatment showed greater reductions in CRP (weighted mean difference [WMD]: −6.299; 95% CI: −9.082 to −3.517), ESR (WMD: −6.563; 95% CI: −8.604 to −4.522), VAS (WMD: −1.089; 95% CI: −1.575 to −0.602), DAS-28 (WMD: −0.633; 95% CI: −1.006 to −0.259), SJC (WMD: −1.921; 95% CI: −3.635 to −0.207), and TJC (WMD: −1.491; 95% CI: −2.941 to −0.042).

Conclusion. This meta-analysis of RA provides reliable evidence in favor of ACNRT plus WM. However, longer term, high-quality, repeatable, multicenter randomized controlled trials with larger sample sizes are needed.

Keywords. Acupuncture; Electro-acupuncture; Meta-analysis, Moxibustion; Rheumatoid arthritis; Systematic review

Journal of the Chinese Medical Association (2022) 85: 414-420.

Lycopene treatment improves intrahepatic fibrosis and attenuates pathological angiogenesis in biliary cirrhotic rats

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Abstract

Background. Liver cirrhosis is characterized by liver fibrosis and pathological angiogenesis, which results in hyperdynamic circulation, portal-systemic collateral vascular formation, and abnormal angiogenesis. Lycopene is a nutrient mostly found in tomatoes. The beneficial effects of lycopene include anti-inflammation, anti-oxidation, anti-fibrosis, and anti-angiogenesis; however, the association between liver cirrhosis and pathological angiogenesis has yet to be studied. This study aimed to investigate the effects of lycopene on biliary cirrhotic rats.

Methods. The efficacy of lycopene treatment in common bile duct ligation (BDL)-induced biliary cirrhotic rats was evaluated. Sham-operated rats served as surgical controls. Lycopene (20 mg/kg/day, oral gavage) or vehicle was administered to BDL or sham-operated rats for 4 weeks, after which the hemodynamics, liver biochemistry, portal-systemic shunting, liver and mesenteric angiogenesis, and hepatic angiogenesis-related protein expressions were examined.

Results. Lycopene alleviated hyperdynamic circulation as evidenced by decreased cardiac index and increased peripheral vascular resistance ($p < 0.05$), but it did not affect portal pressure or liver biochemistry in the BDL rats ($p > 0.05$). Lycopene significantly diminished the shunting degree of portal-systemic collaterals ($p = 0.04$) and mesenteric vascular density ($p = 0.01$), and also ameliorated intrahepatic angiogenesis and liver fibrosis. In addition, lycopene upregulated endothelial nitric oxide synthase, protein kinase B (Akt) and phosphatidylinositol 3-kinases (PI3K), and downregulated vascular endothelial growth factor receptor 2 (VEGFR-2) protein expressions ($p < 0.05$) in the livers of the BDL rats.

Conclusion. Lycopene ameliorated liver fibrosis, hyperdynamic circulation, and pathological angiogenesis in biliary cirrhotic rats, possibly through the modulation of intrahepatic Akt/PI3K/eNOS and VEGFR-2 pathways.

Keywords. Angiogenesis; Hyperdynamic circulation; Liver cirrhosis; Lycopene; Portal hypertension

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Repeated loco-regional therapies for hepatocellular carcinoma is associated with inferior outcome after living donor liver transplantation in cirrhotic patients

Yi-Fan Tsou[a], Niang-Cheng Lin[a,*], Cheng-Yuan Hsia[a,b], Che-Chuan Loong[a,b], Hsin-Lin Tsai[a,c], Cheng-Yen Chen[a], Hao-Jan Lei[a,b], Shu-Cheng Chou[a,b], Meng-Hsuan Chung[a], Fang-Cheng Kuo[a], Chin-Su Liu[a,c]

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Abstract

Background. Liver transplantation is the definitive treatment for defined stage hepatocellular carcinoma (HCC) in cirrhotic patients. Loco-regional therapy (LRT) may be considered before transplantation to prevent the disease progression and the patient from dropping out of the waiting list. This study aims to evaluate the impact of repeated pretransplant LRTs on the long-term outcomes in HCC liver transplant recipients.

Methods. Between 2004 and 2019, living donor liver transplantation (LDLT) recipients with viable HCC on the explant livers were enrolled. Uni- and multivariate analysis was performed with the Cox regression model to stratify the risk factors associated with HCC recurrence and patent survival after LDLT.

Results. A total of 124 patients were enrolled, in which 65.3% (n = 81) were Barcelona Clinic Liver Cancer classification stage B or D and 89% (n = 110) had advanced fibrosis or cirrhosis on the explanted livers. After a median follow-up of 41 months (IQR: 24–86.5), there were 18 cases (13.7%) of HCC recurrence. Univariate analysis showed that the model of end-stage liver disease and Child-Turcotte-Pugh score, pretransplant alpha-fetoprotein value (>500 ng/ml), repeated pretransplant LRTs (N > 4), increased tumor numbers and maximal size, presence of microvascular invasion, and the histological grading of the tumors are risk factors of inferior outcomes. In multivariate analysis, only repeated pretransplant LRTs (N > 4) had a significant impact on both the overall- and recurrence-free survival. The impact of pretransplant LRT was consistently significant among subgroups based on their LRT episodes (N = 0, 1–4, >4 respectively).

Conclusion. Repeated LRT for HCC can be associated with the risk of tumor recurrence and inferior patient survival after LDLT in cirrhotic patients. Early referral of those eligible for transplantation may improve the treatment outcomes in these patients.

Keywords. Hepatocellular carcinoma; Liver transplantation; Living donor liver transplantation; Loco-regional therapy; Outcomes

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Prolonged sitting time links to subclinic atherosclerosis

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Abstract

Background. This study investigates the association between daily sitting time and subclinical atherosclerosis by using coronary computed tomography angiography (CCTA).

Methods. The study enrolled 203 subjects (age 57.6 ± 8.8 years) who underwent CCTA at annual medical checkups. Sitting time was categorized as < 5 hours/day (short), 5 to 9 hours/day (moderate) and ≥10 hours/d (long). We analyzed the coronary calcium score, plaque characteristics, and severity of coronary artery stenosis, including the segment involvement score (SIS) and segment stenosis score (SSS).

Results. Subjects with longer sitting times tended to be male gender and have lower levels of high-density lipoprotein cholesterol (p for trend < 0.05). In addition, those with longer sitting time had higher SIS (1.2 ± 1.5 *vs.* 1.6 ± 2.1 *vs.* 2.3 ± 2.0 for short, moderate, and long sitting time, respectively) (p for trend = 0.015) and SSS (1.4 ± 2.0 *vs.* 1.9 ± 2.7 *vs.* 2.7 ± 2.6) (p for trend = 0.015), suggesting longer sitting time-correlated with the severity of coronary atherosclerosis. When considering the coronary plaque patterns, subjects with shorter sitting time (<5 hours/d) tended to have more calcified plaque and subjects with longer sitting time (≥10 hours/d) had more mixed plaque (p for trend = 0.018). After adjusting for age, gender, comorbidities, body mass index, and lipid profiles, increased sitting time was independently associated with the presence of mixed plaque, suggesting longer sitting time may be associated with higher risk of the formation of vulnerable plaque.

Conclusion. Longer sitting time was linked to the severity of subclinical atherosclerosis and the presence of high-risk vulnerable plaque in the general population.

Keywords. Atherosclerosis; Coronary computed tomography angiography; Coronary plaque; Physical activity; Sitting time

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Effects of nerve-sparing procedures on surgical margins after robot-assisted radical prostatectomy

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Abstract

Background. Nerve-sparing (NS) techniques could potentially increase positive surgical margins after robot-assisted radical prostatectomy (RARP). Nevertheless, the available studies have revealed ambiguous results among distinct groups. This study purposed to clarify the details of NS techniques to accurately estimate their influence on margin status.

Methods. We studied RARPs performed by one surgeon from 2010 to 2018. Surgical margins were evaluated by the laterality and levels of NS techniques in site-specific prostate lobes. The multivariable analysis evaluated the effects of nerve-sparing procedures, combined with other covariate factors, on margin status.

Results. Overall, 419 RARPs involving 838 prostate lobes were analyzed. Notably, 181 patients (43.4%) had pT2-stage, and 236 (56.6%) had pT3-stage cancer. The PSM rates for patients who underwent unilateral, bilateral, and non NS procedures were 30.3%, 28.8%, and 50%, respectively (p = 0.233) or in stratification by pT2 (p = 0.584) and pT3 (p = 0.116) stage. The posterolateral PSM rates among site-specific prostate lobes were 10.9%, 22.4%, and 18.9% for complete, partial, and non NS techniques, respectively (p = 0.001). The partial NS group revealed a significant increase in PSM rate compared with the complete NS (OR 2.187, 95% CI: 1.19–4.03) and non NS (OR 2.237, 95% CI: 1.01–4.93) groups in site-specific prostate lobes.

Conclusion. Partial NS procedures have a potential risk of increasing the positive surgical margins rate than complete and non NS procedures do. Therefore, correct case selection is required before performing partial NS techniques.

Keywords. Margins of excision; Prostatic neoplasms; Prostatectomy; Robotic surgical procedures

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Real-world effectiveness and safety of golimumab in rheumatoid arthritis treatment: A two-center study in Taiwan

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Abstract

Background. The real-world outcomes of golimumab (GLM) use have been rarely studied in Asian patients with rheumatoid arthritis (RA). This study assessed the real-world effectiveness and safety of GLM in a Taiwanese cohort.

Methods. One hundred and eight GLM-treated RA patients were enrolled. Predictors of a good European League Against Rheumatism (EULAR) response at 24 months and drug retention were identified through multivariate analyses.

Results. After 24 months of GLM treatment, the mean Disease Activity Score using 28 joint counts with the erythrocyte sedimentation rate (DAS28-ESR) decreased from 6.7 to 3.1 ($p < 0.001$). Up to 58.9% of patients achieved a good EULAR response at 24 months. Multivariate logistic regression analysis revealed that after adjustment for other variables, a higher baseline C-reactive protein was an independent negative predictor of good EULAR responses (odds ratio, 0.82; 95% confidence interval [CI], 0.67-0.99; $p = 0.043$). During the mean follow-up period of 38.3 months, 15 (13.9%) patients discontinued GLM due to treatment failure. In multivariate analysis, high baseline ESR level, high DAS28-ESR, and the experience of biologic therapy were independent risk factors for GLM discontinuation (adjusted hazard ratio [HR], 1.03; 95% CI, 1.01-1.05; $p = 0.003$; adjusted HR, 2.93; 95% CI, 1.42- 6.08; $p = 0.004$; and adjusted HR, 5.00; 95% CI, 1.75-14.26; $p = 0.003$, respectively). In receiver operator characteristic curve analysis, the optimal cutoff values of baseline ESR and DAS28-ESR for predicting drug survival were 52 mm/h (sensitivity: 60.0% and specificity: 77.4%) and 7.7 (sensitivity: 46.7% and specificity: 94.3%), respectively. During the follow-up period, 22 patients (20.4%) developed adverse events. The safety profile of GLM in this study was comparable with that in previous clinical trials.

Conclusion. GLM was effective and safe for the real-life management of Taiwanese RA patients and showed a high retention rate in biologic-naive patients compared with biologic-experienced patients.

Keywords. Efficacy; Golimumab; Real-world data; Safety; Tumor necrosis factor

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Risk factors of recurrent carotid blowout syndrome and strategy of endovascular management

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Abstract

Background. Carotid blowout syndrome (CBS) is a catastrophic complication after aggressive head and neck cancer treatment. Endovascular embolization is an effective modality to manage CBS. However, some CBS may have recurrent CBS (rCBS) after endovascular management. This study aims to report the potential rCBS risk and endovascular management strategy.

Methods. Of the 225 patients with CBS referred for embolization in 13 years, 31 men and one woman (mean age, 55 years) with 35 rCBS with pseudoaneurysms formation were identified after endovascular management. Moreover, the rCBS preembolization angioarchitecture, rCBS cause, rCBS time interval, embolic materials selection, and final embolization clinical/angiographic outcomes were retrospectively analyzed.

Results. rCBS with pseudoaneurysm due to disease progression (DP) occurred in 17 patients, while 15 patients had insufficient embolization (IE) with 18 rCBS. The mean rCBS timing interval was 76 days with 129 and 12 days due to DP or IE. The most common rCBS locations were the carotid bulb and the main trunk of the external carotid artery (n = 20, 57%), followed by internal carotid artery (n = 8, 23%), distal branch of the external carotid artery (n = 4, 11%), and common carotid artery (n = 3, 9%). Endovascular management was technically successful in all patients by reconstruction (n = 7, 20%) or destruction (n = 28, 80%) techniques. Three patients (9%) had procedure-related complications. No rCBS was observed in all affected arteries after the last embolization in a mean 11-month clinical follow-up.

Conclusion. rCBS may result from DP or IE. The common location of IE-related rCBS usually occurred in the carotid branches. It occurred within two weeks of CBS largely because of the underestimation of the extension of the affected carotid artery. In addition, DP is natural in head and neck cancer after aggressive treatment. Thus, endovascular management remained an effective method to manage rCBS.

Keywords. Carotid blowout syndrome; Embolization; Head-neck cancer; Recurrence

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Efficacy of cetuximab-containing regimens in the treatment of recurrent/metastatic head and neck cancer after progression to immune checkpoint inhibitors

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Abstract

Background. The antiepidermal growth factor receptor (EGFR) monoclonal antibody cetuximab and immune checkpoint inhibitors (ICIs) are the current front-line treatment for recurrent and metastatic head and neck squamous cell carcinoma (R/M HNSCC). However, understanding of the efficacy of cetuximab-containing regimens in patients who fail ICI treatments is limited. In this study, we present the efficacy of cetuximab-based regimens in heavily pretreated R/M HNSCC patients after progression to ICIs.

Methods. This was a retrospective study that analyzed patients diagnosed with R/M HNSCC who progressed after ICIs and then received their first-time cetuximab-based regimens at Taipei Veterans General Hospital from January 2017 to December 2020. The response rate, overall survival, and progression-free survival were measured.

Results. A total of 28 patients were included in this study. Most patients had received pembrolizumab as an ICI. The median duration of cetuximab-based regimens prescribed was 4.5 months. The objective response rate (ORR) was 32.1% (95% confidence interval [CI], 17.9%-50.6%), and the disease control rate (DCR) was 53.6% (95% CI, 42.4%-76.4%). The median overall survival and median progression-free survival were 9.1 months (95% CI, 1.3-16.8) and 2.9 months (95% CI, 2.2-3.5), respectively. The incidence of cetuximab-related adverse events was reported as 39.2%.

Conclusion. A cetuximab-based regimen is still an effective and tolerable treatment for R/M HNSCC after progression on ICIs. Future prospective studies are needed to identify better treatments for previously ICI-treated or heavily treated R/M HNSCC patients.

Keywords. Cetuximab; Head and neck cancer; Immune checkpoint inhibitors

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Clinical outcomes and metastatic behavior between de novo versus recurrent HER2-positive metastatic breast cancer: A 17-year single-institution cohort study at Taipei Veterans General Hospital

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Abstract

Background. To assess the clinical outcomes and metastatic behavior between de novo versus recurrent human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC) based on a single-institution database in Taiwan.

Methods. We retrospectively identified patients diagnosed between January 2000 and December 2017 with de novo stage IV or recurrent HER2-positive MBC. Several variables were recorded in patients with recurrent disease: age at diagnosis, metastatic site, hormone receptor (HR) status, HER2 status, and disease-free interval (DFI). Treatments and metastatic patterns were compared between de novo stage IV and recurrent MBC cohorts. Post-metastasis survival (PMS) was estimated using the Kaplan-Meier method with log-rank tests. Hazard ratios and 95% CIs were estimated using Cox regression analysis.

Results. In total, 1360 patients were diagnosed with breast cancer with HER2 overexpression. At baseline, de novo stage IV patients were older than recurrent MBC patients (median age 58 vs 53). The majority of the de novo stage IV patients were diagnosed after 2010, while most of the recurrent MBC patients were diagnosed during 2000-2009. An increased number of de novo stage IV patients underwent targeted therapy than recurrent MBC patients was also noted. PMS in patients with de novo stage IV and recurrent MBC was 79.2 months and 61.8 months, respectively, which indicated significant better survival in de novo stage IV than those with recurrent MBC disease. Longer survival was also noted in de novo stage IV

and recurrent MBC with DFI >24 months than in those with recurrent MBC with DFI <24 months and in patients receiving HER2-targeted therapy after MBC diagnosis than in those not receiving the therapy. However, median PMS showed no significant difference between patients with the luminal B2 (HR-positive, HER2-negative) and HER2-enriched (HR-negative, HER2-positive) subtypes. After adjustment in multivariate analysis, a low risk of BC-specific death was observed in patients aged >50 years, those receiving HER2-targeted therapy for MBC, and those with oligometastasis, while patients with first metastases to the liver or brain showed a higher risk of BC-specific death than those without metastases.

Conclusion. De novo and recurrent MBC have distinct characteristic, metastatic patterns and outcomes in Asian HER2-positive breast cancer patients. The age distribution and survivals between HR+/– status were different to non-Asian group. These differences should be further investigated in the future considering ethnic factor.

Keywords. Breast cancer; HER-2 protein; Metastasis; Post-metastasis survival; Recurrence

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Potential therapeutic agents against COVID-19: What we know so far

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Abstract

The emerging outbreak of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 continues to spread all over the world. Agents or vaccines of proven efficacy to treat or prevent human coronavirus infection are in urgent need and are being investigated vigorously worldwide. This review summarizes the current evidence of potential therapeutic agents, such as lopinavir/ritonavir, remdesivir, favipiravir, chloroquine, hydroxychloroquine, interferon, ribavirin, tocilizumab, and sarilumab. More clinical trials are being conducted for further confirmation of the efficacy and safety of these agents in treating COVID-19.

Keywords. Chloroquine; COVID-19; Favipiravir; Hydroxychloroquine; Interferon; Lopinavir/ritonavir; Remdesivir; Ribavirin; Sarilumab; Severe acute respiratory syndrome coronavirus 2; Tocilizumab

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Reference:
1.PHESGO 最新版仿單
2.Tan AR, et al. Lancet Oncol 2020
3.Joyce O'Shaughnessy, et al. Eur J Cancer 2021

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副作用: 由於臨床試驗進行的條件變異很大，在藥物臨床試驗中觀察到的不良反應率無法直接與另一項藥物臨床試驗中的不良反應率相比較，且無法反映實際觀察到的不良反應率。靜脈輸注之Perjeta (pertuzumab)與Herceptin (trastuzumab)給藥後曾通報下列不良反應：腹瀉、禿髮、噁心、疲倦、嗜中性白血球減少症、嘔吐、周邊神經病變、便秘、貧血、無力、黏膜發炎、肌痛和血小板減少症。

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達到心臟 LVMi 顯著降低、腎臟功能維持穩定等多重器官臨床指標*

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加厲伏藥品處方資訊摘要：1. **藥品名稱：**加厲伏膠囊 123 毫克 (**衛部罕藥輸字第 000060 號**) 2. **主要成分：**每粒膠囊內含 migalastat hydrochloride，相當於 migalastat 123 毫克 3. **治療適應症：**加厲伏 適用於已確診為法布瑞氏症且於體外試驗確定為可符合性基因突變 (amenable mutation) 的 16 歲 (含) 以上病人。4. **劑量與給藥方式：**加厲伏 應由具有診治法布瑞氏症經驗的專科醫師監督給藥。加厲伏 不適合與酵素替代療法同時給藥。．**劑量：**成年病人與 16 歲以上 (含 16 歲) 青春期病人的 加厲伏 建議劑量為每間隔 1 日 1 次，每次在固定的時間服用 加厲伏 123 毫克 (1 粒)．**給藥方式：**口服給藥。加厲伏與食物併用時，在體內的暴露量大約減少 40%，因此飯前與飯後 2 小時內不可服用加厲伏，這樣病人至少有 4 小時空腹狀態，這段時間內病人可以飲用包含碳酸飲料在內的澄清的流質飲料。對病人最好的方式是每間隔 1 日 1 次，每次在固定的時間服用加厲伏。加厲伏膠囊應整粒吞服，不可切開、碾碎或咀嚼。**加厲伏仿單中禁忌、警告與注意事項 4.3 禁忌** 對主成分或對仿單中第 6.1 節內所列出的賦形劑過敏者禁用。**4.4 警告與注意事項** 已開始使用或改用 migalastat 的病人應定期 (每 6 個月) 監測腎功能、心電圖與生化檢驗。當臨床狀況明顯惡化時，應再度作臨床評估或考慮停用加厲伏。加厲伏不適用於具有非可符合性突變的病人 (參見仿單中第 5.1 節)。未曾看到以加厲伏治療的病人有蛋白尿減少的情形。嚴重腎功能不全 (腎絲球過濾率小於 30 mL/min/1.73 m^2) 的病人，不建議使用加厲伏 (參見仿單中第 5.2 節)。有少數的資料顯示加厲伏單次劑量與一次輸注標準酵素取代療法併用會造成 agalsidase 在體內動態濃度最多增加達到 5 倍。該試驗也指出 agalsidase 不影響 migalastat 的藥品動力學。加厲伏不適合與酵素替代療法同時給藥。**4.5 與其他藥物的交互作用以及各種形式的交互作用** 依據體外實驗資料，migalastat 不是 CYP1A2、2B6 或 3A4 的誘導劑。而且，migalastat 也不是 CYP1A2、2A6、2B6、2C8、2C9、2C19、2D6、2E1 或 3A4/5 的受質或抑制劑。Migalastat 不是 MDR1 或 BCRP 的受質，也不是 BCRP、MDR1 或 BSEP 等人類外排轉運蛋白的抑制劑。此外， migalastat 不是 MATE1、MATE2-K、OAT1、OAT3 或 OCT2 的受質，也不是 OATP1B1、OATP1B3、OAT1、OAT3、OCT1、OCT2、MATE1 或 MATE2-K 等人類攝入轉運蛋白的抑制劑。**4.6 生育、懷孕與授乳** 可能懷孕的女性病人/男性與女性病人的避孕 有可能懷孕且未避孕的女性病人不可使用加厲伏。懷孕 孕婦服用 加厲伏 的資料很少。在兔子試驗中觀察到，只有達到對雌兔有毒性劑量時才出現生長發育毒性(參見仿單中第5.3節)。懷孕期間不可服用 加厲伏。餵奶 未知加厲伏是否會排放於人類乳汁中，不過，曾發現 migalastat 出現於正在餵奶的大鼠乳汁中，因此，喝母奶的嬰兒也可能有暴露於 migalastat 的風險。應衡量母親接受加厲伏治療的效益與餵奶帶給嬰兒的風險何者重要，來決定應停止餵奶或停用加厲伏。生育 未曾研究 加厲伏 對人類生育力的影響。實驗顯示雄性大鼠接受所評估的各劑量之 migalastat 後，出現短暫不孕。藥物停用 4 週後可以完全恢復生育能力。其他 iminosugars 治療的前臨床實驗也有類似的結果 (參見仿單中第 5.3 節)。加厲伏不影響雌性大鼠的生育能力。**4.7 對駕駛與操作機具的影響** 加厲伏對駕駛或操作機具的能力無影響或影響極小。**4.8 不良反應** 安全性摘要 加厲伏最常見的副作用是頭痛，大約有 10% 病人出現頭痛。副作用列表 發生頻次類別的定義為：極常見 (≥1/10)、常見 (≥1/100 到 <1/10)、少見 (≥1/1,000 到 <1/100)、罕見 (≥1/10,000 到 <1/1,000)、極罕見 (<1/10,000) 以及不明 (現有資料無法估算)。在每種頻次類別中，依據系統器官分類將副作用發生率由高至低順序排列。表一、完整的不良反應列表，請參見仿單。疑似副作用的通報　藥品批准上市後的疑似副作用通報相當重要，如此可持續監測該藥品的效益/風險平衡。專業醫護人員必須將所有疑似副作用透過全國副作用通報系統進行通報。**4.9 過量中毒**　若發生過量中毒，應給予一般性醫療處置。當加厲伏用量達到 1250mg 或 2000mg 時，最常出現的副作用報告分別是頭痛與頭暈。

詳細處方資料備索、僅供專業醫療人員參考

*** References:** Galafold 藥品仿單。

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Reference :
1. Lancet. 1998;352:854-65 2. N Engl J Med. 2008 Oct 9;359(15):1577-89 3. FDA藥字第1110019277號
UKPDS+：英國前瞻性研究 (UK Prospective Diabetes Study)

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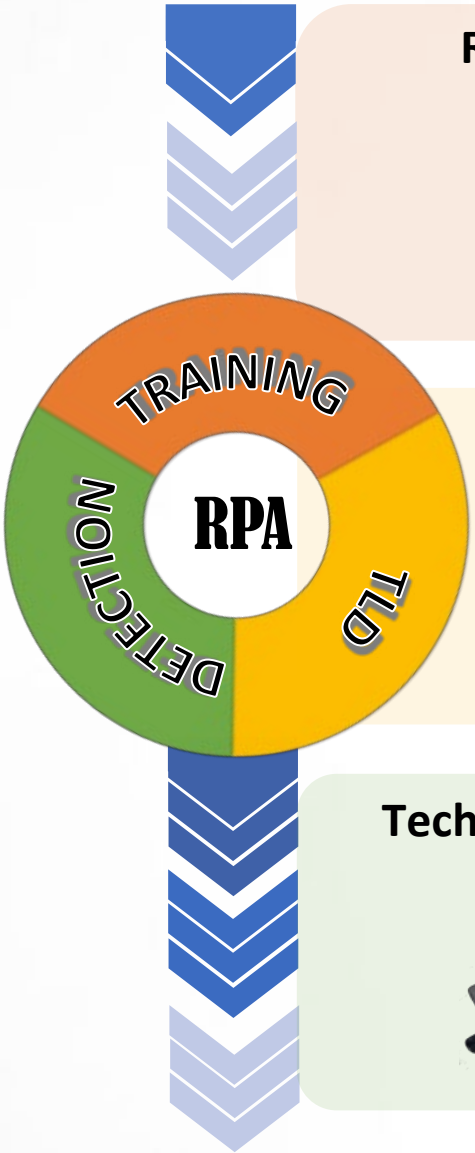

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*與glargine相較 **Ref: 1.** Rosenstock, Julio et al. Diabetes care vol. 39,11 (2016): 2026-2035. doi:10.2337/dc16-0917 **2.** Yang, Wenying et al. Diabetes, obesity & metabolism, 10.1111/dom.14722. 19 Apr. 2022, doi:10.1111/dom.14722 **3.**中華民國糖尿病學會2022年第2型糖尿病臨床照護指引 http://www.endo-dm.org.tw/dia/

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【產品名稱】爽胰達注射劑100單位+50微克Soliqua solution for injection 100 units +50 μg **【主要成分】**每支預填注射筆3 mL溶液內含有insulin glargine*300 units及lixisenatide 150 μg。每 mL含有insulin glargine 100 units及lixisenatide 50 μg。每個劑量單位含有insulin glargine 1 unit及lixisenatide 0.5 μg。

[處方資訊摘要]

【適應症】適用於當metformin合併使用另一種口服降血糖藥或metformin合併使用基礎胰島素(每日劑量少於60單位)治療時血糖控制不佳的第二型糖尿病成人病人，在飲食與運動外，做爲改善血糖之輔助治療。適用於當metformin合併使用類升糖素胜肽-1(GLP1-1)受體促效劑或metformin 和另一種口服降血糖合併使用類升糖素胜肽-1 (GLP1)受體促效劑治療時血糖控制不佳的第二型糖尿病成人病人，在飲食與運動外，做爲改善血糖之輔助治療。適用於基礎胰島素(每日劑量少於60單位)或lixisenatide治療時血糖控制不佳的第二型糖尿病成人病人，在飲食與運動外，做爲改善血糖之輔助治療。**【用法用量】**Soliqua100 units/mL + 50 μg/mL預填注射筆可提供insulin glargine 10-40 units合併lixisenatide 5-20 μg之劑量單位。劑量:劑量應依照個人的臨床反應及病人對胰島素的需求作調整。Lixisenatide的劑量會隨著 insulin glargine 的劑量而有所增加或減少且視所使用的注射筆而定。起始劑量:Soliqua開始給藥前應先停用基礎胰島素、lixisenatide或其他類升糖素胜肽-1(GLP-1)受體促效劑。因Soliqua併用metformin及SGLT-2抑制劑以外的口服降血糖藥安全性資料(包括低血糖)有限，因此提醒臨床醫師在首次使用Soliqua前，建議停用病人目前的口服降血糖藥物(若爲metformin或SGLT-2抑制劑則不需停用)，待確認安全性無疑慮後再開始併用口服降血糖藥物。Soliqua的起始劑量乃依先前的抗糖尿病治療而定，且lixisenatide的起始建議劑量不得超過10 μg，即Soliqua的起始建議劑量不得超過20個劑量單位

先前治療	未使用過胰島素 (口服降血糖藥或GLP-1 受體促效劑)	Insulin glargine (100 units/ml)**	Insulin glargine (100 units/ml)**
		<20 units	≥20 – <30 units
Soliqua 起始劑量	10 個劑量單位(10 units/5 μg)*		20 個劑量單位(20 units/10 μg)*

* units insulin glargine (100 units/mL) / μg lixisenatide **若使用不同的基礎胰島素：•若基礎胰島素爲每日給藥2次或使用每日一次insulin glargine (300 units/mL)，則先前給藥的每日總劑量應下調20%以作爲Soliqua 起始劑量。• 任何其他基礎胰島素的計算方式與insulin glargine (100 units/mL)相同。劑量調整: Soliqua的劑量應依照個別病人對胰島素的需求給藥。建議依據空腹血糖值調整劑量以使血糖獲得最佳控制。• Soliqua 最高劑量可調整至40個劑量單位。**【禁忌】**對活性成分或章節6.1所列之任何賦形劑過敏者。**【警語及注意事項】**Soliqua不可使用於第一型糖尿病病人或用於治療糖尿病酮酸中毒。Soliqua治療期間最常見的不良反應爲低血糖，Soliqua 的劑量應依照個人的臨床反應及病人對胰島素的需求作調整。使用類升糖素胜肽-1 (GLP-1)受體促效劑被認爲與發生急性胰臟炎的風險相關。應告知病人急性胰臟炎的特徵症狀。若懷疑發生胰臟炎，應停用Soliqua；若確定爲急性胰臟炎，lixisenatide不可重新投藥。有胰臟炎病史的病人使用時應小心。Soliqua未曾針對嚴重胃腸道疾病病人做過研究，包括嚴重胃輕癱(gastroparesis)，因此Soliqua不建議使用於這類病人。倘無使用於嚴重腎功能不全或末期腎病病人之治療經驗。本品不建議使用於嚴重腎功能不全或末期腎病病人。接受Soliqua治療有發生脫水的潛在風險，此與胃腸道不良反應有關，因此應小心以避免體液流失。Soliqua注射有可能導致 insulin glargine 及/或lixisenatide抗體之形成。須指示病人對注射部位進行持續轉換，以減少發生脂肪代謝障礙(lipodystrophy)和皮膚澱粉樣變性症(cutaneous amyloidosis)的風險**【交互作用】** Insulin glargine有些藥物可能會影響葡萄糖的代謝，因此可能需要調整insulin glargine的劑量。併用口服抗糖尿病藥、ACE抑制劑、disopyramide、fibrates、fluoxetine、MAO抑制劑、pentoxifylline、propoxyphene、水楊酸鹽、或磺胺類抗生素等，都可能會增加降血糖效果而容易造成低血糖症。併用皮質類固醇、danazol、diazoxide、利尿劑、glucagon、isoniazid、雌激素及黃體素phenothiazine衍生物、somatropin、擬交感神經作用藥、甲狀腺荷爾蒙、非典型抗精神病藥物或蛋白質酵素抑制劑可能會減弱降血糖效果。β-抑制劑、clonidine、鋰鹽或酒精可能會加強或減弱胰島素的降血糖效果;而pentamidine可能造成低血糖症，有時候又接著發生高血糖症。此外，β-抑制劑、clonidine、guanethidine、reserpine等藥物由於其交感神經抑制作用，可能會減弱或甚至完全抑制腎上腺反調節機制。Lixisenatide:Lixisenatide是一種胜肽且不會被細胞色素P450所代謝。在體外試驗中，lixisenatide不會影響細胞色素P450同功酶或人體運輸蛋白 (human transporters) 的活性。lixisenatide延緩胃排空可能會降低口服藥物的吸收速率。當併用治療範圍狹窄或需要臨床上小心監測的口服藥物時應謹慎使用。與lixisenatide併用時，應適當監測這些藥物。若這些藥物要與食物併服，應告知病人盡量選擇未注射lixisenatide的那一餐或點心時間服用這些藥物。若口服藥物必須達到特定濃度閾值才具有療效，例如抗生素，或會造成延遲效果的藥物，例如acetaminophen，則併服該藥物時，必須至少在lixisenatide注射前1小時服用。使用口服避孕藥之病人，必須至少在lixisenatide注射前1小時或注射後11小時服用。**【生育能力、懷孕及哺乳】**Soliqua不應在懷孕期間使用。若病人想要懷孕或已經懷孕，應停用Soliqua。哺乳:Insulin glargine 或 lixisenatide 是否會從人類乳汁中分泌仍不得而知。Soliqua不可在哺乳期間使用。**【不良作用】**極常見：低血糖。常見：頭暈、噁心、腹瀉、嘔吐。 注射部位反應:局部水腫及發癢的情形。**【過量】**若病人的Soliqua給藥劑量高於需求量，則有可能發生低血糖及胃腸道不良反應。 仿單版本 CCDS v3_14Feb2019 + CCDS v4_10SEP2020

本印刷品製作日期: 07. 2022
北市衛藥廣字第111070128號

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台北市信義區11010松仁路3號7樓
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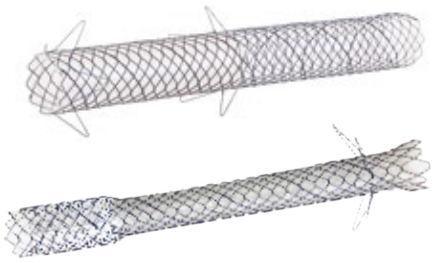

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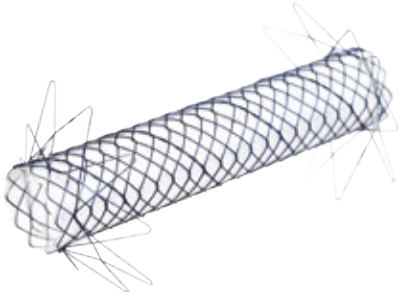

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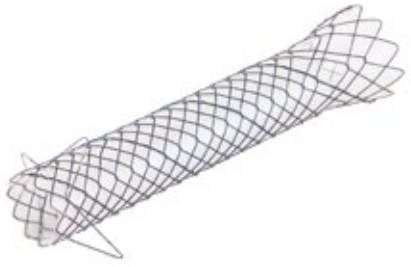

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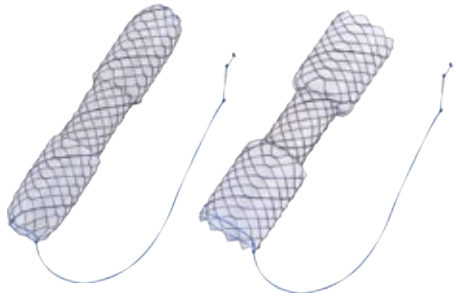

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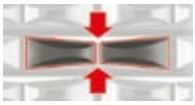

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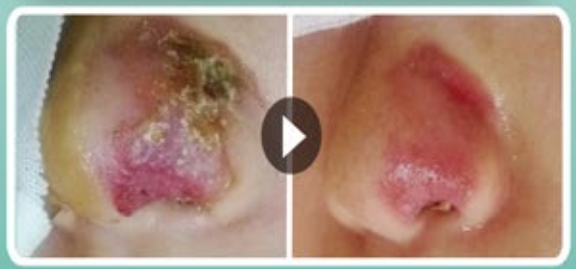
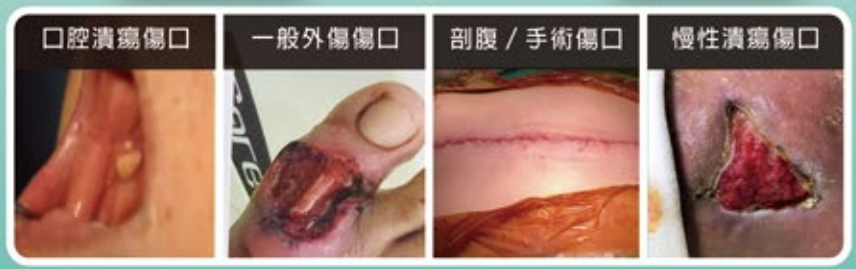


▲鼻子嚴重創傷，使用jeancean液態傷口噴霧照護，3天後表皮癒合，復原狀況良好。



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・美國專利局核發此技術，根據市調公司IQVIA在2020年的調查
・衛部醫器輸字第034053號，北市衛器廣字第110060043號
・使用前請詳閱說明書警語及注意事項，諮詢請洽各大醫療院所、藥局 TW-SYH-2100017

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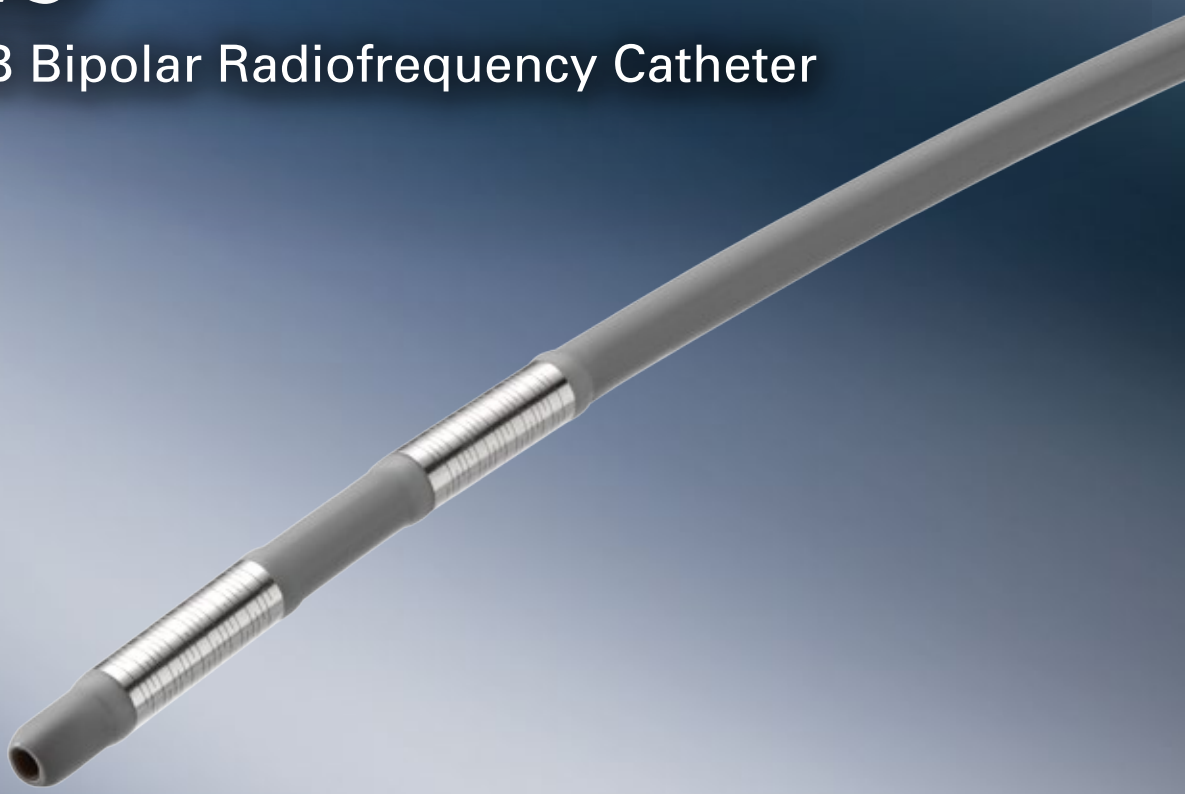

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- Ablation of benign or malignant tissue
- To perform endoscopic biliary decompression prior to stent placement or afterwards

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