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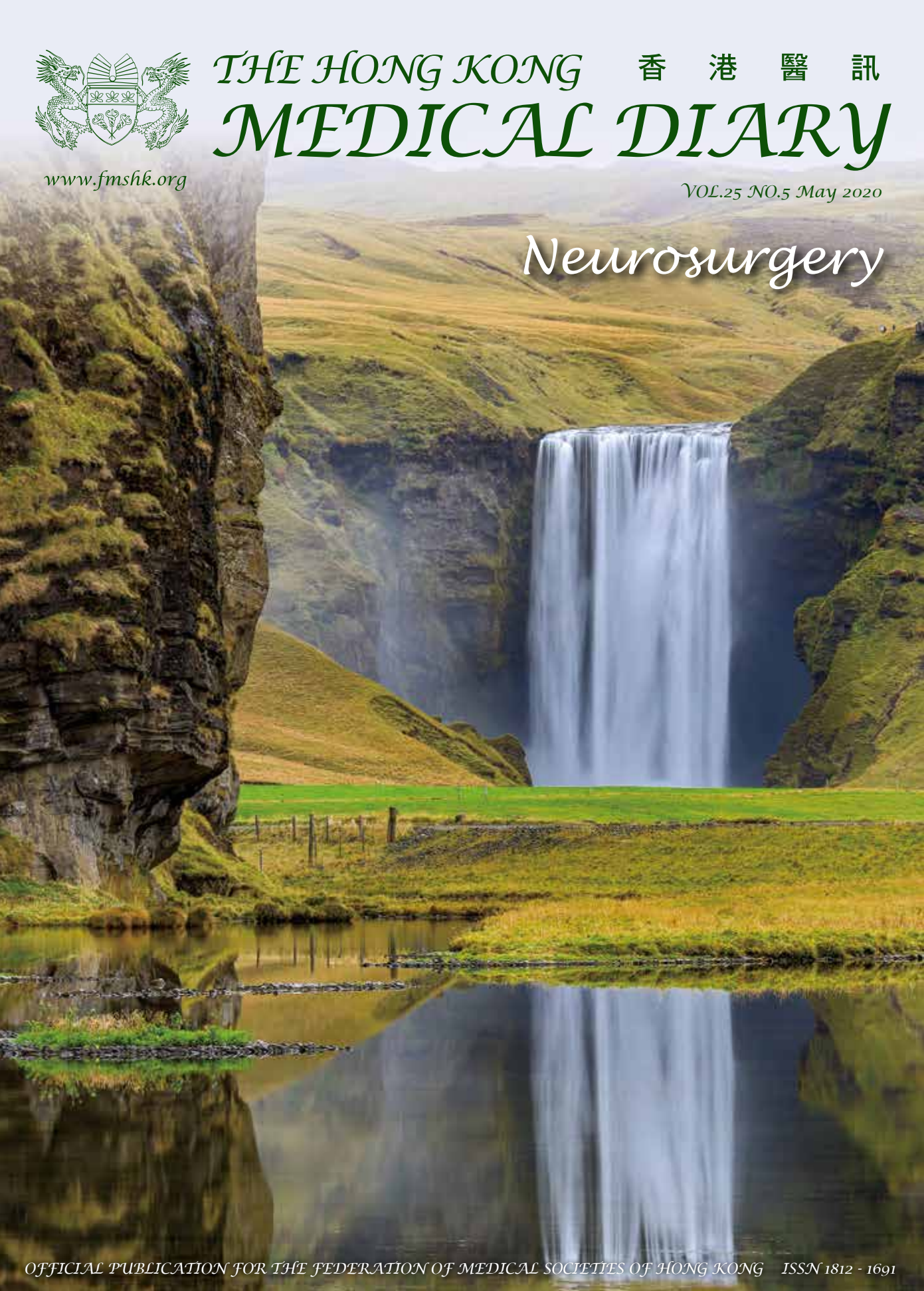

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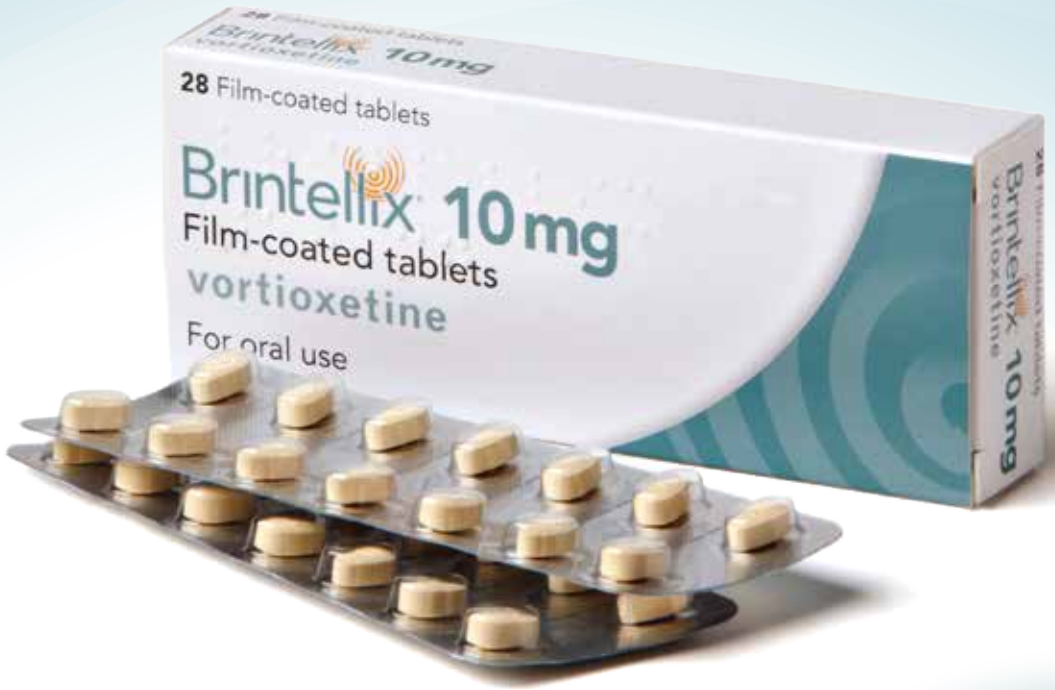

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The Cover Shot

Skogafoss waterfall is one of the largest and most elegant waterfalls in Iceland. It is also known as Rainbow waterfall because it generates a lot of sprays which often creates a single or double rainbow on sunny days.

This picture was taken early in the morning when the site was not cramped with tourists. A perfect crystal-clear reflection can only be obtained if you are lucky enough to have fine weather and the wind is not too strong.

My gear: Canon EOS R with
EF 70-300mm f/4.5-5.6L IS USM
Exif: 0.5s, f/25, ISO100 with tripod.

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Editorial

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Editor

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This issue of the Medical Diary has gathered the efforts from neurosurgical colleagues who are specialist neurosurgeons with subspecialty development and interest. They have introduced to us the recent advances in their subspecialty field and how cutting-edge technologies improve patient care, empowering us in curing neurological diseases with reduced operative morbidities.

The contemporary management of the most common malignant brain tumour, brain metastasis, will be covered. The incidence of metastatic brain tumour is showing a gradual increase, partly because of the gradual increase in incidence of malignancies, but more importantly because malignancies have been transformed into chronic diseases due to the advancement in chemotherapy and targeted therapy. Cancer survivors should be subjected to CNS surveillance. Using avant-garde stereotactic radiosurgery (SRS) software, noninvasive treatment of multiple metastases in a single session is possible and the role of whole brain radiotherapy is thus diminishing. Patients of SRS can survive with better cognitive functions.

Two papers in this issue have been devoted to functional neurosurgery. Deep brain stimulation involves the use of stereotactically placed electrode in a carefully selected target in the basal ganglia; electric stimulation achieves neuromodulation and can control symptoms of patients suffering from movement disorders such as tremor, Parkinson disease and primary dystonia. The indications are now extended to cover intractable epilepsy, compulsory offensive disorders and other neuropsychiatric disorders. The evidence supporting other clinical usage is also accumulating.

Epilepsy surgery work-up is indicated in patients suffering from intractable epilepsy. We have adopted and used various pre-surgical and surgical strategies to locate and to remove the epileptogenic focus. An in-depth description of how a reiterated technique, Stereotactic Electroencephalography (SEEG), can help localising epileptogenic foci and seizure propagation pathways making subsequent epilepsy surgery possible.

Neuro-spine is another territory neurosurgeons are committed to. Minimally invasive techniques are used for decompression or instrumentation. Minimally invasive approach is further elaborated by the use of the endoscopic technique in managing lumbar spinal stenosis and for decompressing the herniated disc. Patient selection and the limitations on endoscopic approaches are discussed.

Neurosurgeons in Hong Kong have been performing neuro-interventional procedures using endovascular technique for more than two decades. Treatments for cerebral aneurysms, arteriovenous malformation and dural AV fistulas are well established. The MRCLEAN study has provided evidence and heralded the use of intra-arterial thrombectomy for the treatment of ischaemic stroke caused by major intracranial artery occlusion. A very comprehensive review and discussion on the latest development of neuro-interventional procedures will be presented.

Finally, we introduce artificial intelligence (AI) and deep learning into the field of neurosurgery. The use of AI covers every step of our patient care, from diagnosis to surgery planning and implementation. The protagonist of AI will flourish, and we have to embrace, adopt and make the best use of this knowledge.


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Deep Brain Stimulation Beyond the Movement Disorders

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 May 2020.

INTRODUCTION

Deep brain stimulation (DBS) involves the implantation of electrodes into specific targets of the brain allowing conduction of electrical impulses from an implanted neurostimulator to the targets. History of DBS has evolved from intended electrical stimulation or ablative procedures to treating various psychiatric and movement disorders. DBS has become renowned for its use on movement disorders, especially Parkinson's disease and dystonia. Apart from that, there is an expanding use of DBS in other fields, including epilepsy and psychiatric disorders. Currently, approved indications for DBS include Parkinson's disease, essential tremor, primary dystonia, obsessive-compulsive disorder and partial seizures. Other potential applications include depression, minimally conscious state and cognitive disorders. This article will focus on applications of DBS beyond movement disorders.

DRUG-RESISTANT EPILEPSY

The role of DBS in drug-resistant epilepsy (DRE) dated back to 1970s and 1980s when studies were published on DBS for DRE. The mechanism of action remains poorly understood, possibly involving upregulation of GABA activity or neurostimulation of neurons, glial cells, passage fibres or afferent inputs to target neurons.

Target and Efficacy

Theories behind DBS for DRE include stimulating the epileptogenic zone and interrupting subcortical epileptic pathway and deep white matter tract.[1]

The anterior nucleus of the thalamus is the most commonly used target given its role in connecting fornix and mammillothalamic tract to the limbic cortex. Significant reduction in seizure frequency up to 70% has been reported.[2] Another thalamic target would be the centromedian nucleus, especially in primary or secondary Lennox Gastaut syndrome.[3]

Both cerebellar cortex and cerebellar nuclei as targets of DBS have been described in literature given its inhibitory nature through Purkinje cells. However, relatively small sample sizes, conflicting results and complications including lead migration, wound infection and mechanical failure have limited its role in the treatment of epilepsy.

Other reported targets include subthalamic nucleus, caudate nucleus and hippocampus.

In contrast to DBS for movement disorders where stimuli are continuous, closed-looped stimulation has been studied where responsive neurostimulation would be delivered when a seizure is detected.

PERSISTENT VEGETATIVE STATE/ MINIMALLY CONSCIOUS STATE

Case reports exist regarding the application of DBS to the persistent vegetative state (PVC) or minimally conscious state (MCS). PVC is defined by the Multi-Society Task Force as a condition of wakefulness without awareness, no evidence of purposeful behaviours to external stimuli, lack of language comprehension and expression with preservation of sleep-wake cycles and certain autonomic functions. In MCS, conscious awareness is partially preserved.

Target and Efficacy

DBS for PVC/MCS was first described by McLardy in 1968, when a patient diagnosed as "coma vigilans" after head injury was operated targeting left thalamus.[4] Literature concerning this application is still lacking and limited to case series. Centromedian - parafascicular nuclei remains a commonly employed target.

There is limited evidence concerning which side to operate on. Usually the left side or the less damaged side from the underlying pathology will be chosen. Extensive workup before the operation is usually done using electrophysiological and radiological evaluation.

Schiff has contributed to early experimental work by publishing a single-subject study featuring a patient with severely injured brain benefiting from central thalamic DBS. Relationship of stimulation ON and OFF was studied featuring a "wash-out" effect on oral feeding and a "carry-on" effect on object naming. This

study provided an early model of studying the effect of stimulation of central thalamus on minimally conscious state and rehabilitation.[5,6]

The reported success rate is around 14% - 30%. In a recent series by Chudy, four out of fourteen patients improved after the operation.[7] Two MCS patients regained consciousness and regained their ability to walk, speak fluently, and live independently. One MCS patient reached the level of consciousness but was still wheelchair-bound. One VS patient (who had suffered a cerebral ischemic lesion) improved to the level of consciousness and responded to simple commands. Improvement of consciousness was off after stimulation was off.

Controversy

The procedure has been highly controversial given the ethical considerations, especially consent and funding. After-care from relatives is also important in a patient's rehabilitation. The reported time frame from initial insult to the time of DBS ranges from 17 days to 21 years. There is concern that improvement of consciousness would be attributed to spontaneous recovery; as such, there is a need for trials with control arm to eliminate the confounding factors.

ALZHEIMER'S DISEASE

Alzheimer's disease is a common chronic neurodegenerative disease and poses a great socioeconomic problem to the society. As conventional pharmacological treatment carries limited efficacy, there is a need for alternative therapies. DBS for Alzheimer's disease and dementia came to attention when Hamani attempted bilateral hypothalamic DBS on patients with obesity and noticed they reported déjà vu episodes. Postoperative imaging showed that the electrodes were close to the fornix and were the likely cause of the symptoms. Hypotheses for the underlying mechanism include 1) enhanced neurotransmission via an increase in acetylcholine release; 2) enhanced neurogenesis; 3) release of neurotrophic factors; and 4) restoring abnormal network activity.[8]

Target and Efficacy

Among the components of memory structures, fornix and nucleus basalis of Meynert have remained the popular targets for researchers. In the early series of Laxton, 6 patients underwent fornix stimulation showing an improvement in cognitive function and a decrease in the rate of decline of Mini-Mental State Examination (MMSE) score.[9] Subsequent series from Fontaine and Lozano also showed slowing of cognitive decline in patients undergoing fornix stimulation.[10,11] Stimulation of nucleus basalis of Meynert also resulted in cognitive improvement in case series, especially in younger age and earlier disease stage.[12,13] Stimulation of ventral capsule/ventral striatum has also been reported.[14] So far, the role of DBS in cognitive disorders is still under investigation. Several clinical trials are ongoing in London, Rouen and China.

OBSESSIVE COMPULSIVE DISORDER

Obsessive compulsive disorder (OCD) is the first Food and Drug Administration (FDA)-approved psychiatric disorder for DBS. Several well-conducted trials have demonstrated the benefits of active stimulation, with the response rate in the 50 to 80% range.

Pathophysiology

The theory of OCD started in the 1980s from the identification of cortical-basal ganglia-thalamocortical circuits conveying information along the cortex, striatum, pallidum, subthalamic nucleus and thalamus.[15] Subsequently, different circuits including orbitofrontal cortex (OFC), dorsolateral prefrontal cortex and anterior cingulate cortex have been reported. Both hyperactivity and hypoactivity of the circuits can lead to an exaggerated attention to perceived threat, contributing to obsession and cognitive inflexibility.[16]

Patient Selection

The primary diagnosis of OCD should be established by psychiatrists. Eligible patients would be at least 5 years from initial diagnosis. During this period of 5 or more years, the patient should receive three trials of ≧ 12 weeks of maximally tolerated doses of serotonin reuptake inhibitors (selective or not), including one trial of clomipramine, at least two augmentation strategies such as the use of antipsychotics or tricyclic antidepressants, and at least 20 hours of expert OCD specific exposure/response prevention (ERP) therapy (shorter duration is allowed if nonadherence is due to intolerance of therapy). Disease severity would be assessed by using Yale Brown Obsessive Compulsive Scale (YBOCS). Majority of literatures used a minimum score of 28, or 14 if only obsessions or only compulsions are present.[17]

Target and Efficacy

On literature review, a number of studies using different targets have been identified. A majority of the studies target anterior limb of the internal capsule (ALIC)[18,19] or ventral capsule/ventral striatum (VC/VS)[20,21], albeit using a variety of nominal target names including nucleus accumbens, bed nucleus of stria terminalis (BNST), inferior thalamic peduncle (ITP). These names are targets within the same region with small variations where studies suggested the actual target would be the white matter fibre tract passing through the region. Another target would be the subthalamic nucleus (STN)[22], a target commonly used in DBS for Parkinson's disease.

Since the first report by Nuttin in 1999 describing the use of DBS on patients with OCD targeting ALIC, subsequent trials have been carried out with a response rate around 50-80%. The recent trial by Tyagi targeting both STN and VC/VS achieved a response rate of 83%.[23] Among various studies, no adverse effects or cognitive impairment have been observed.

DEPRESSION

Major depressive disorder (MDD) is a common psychiatric disease impairing the patient's ability to work and imposing social and financial issues in society. Despite the availability of antidepressants and psychotherapy, only around a third of patients with MDD would enter complete and sustained remission.[24] Treatment-resistant depression (TRD) is commonly defined as an episode of major depression that has not improved after at least two adequate trials of different classes of antidepressants. An effective option for TRD would be electroconvulsive therapy (ECT). However, ECT needs to be performed under general anaesthesia and is associated with more cognitive side effects. Other treatment options include transcranial magnetic stimulation, transcranial direct current stimulation and vagal nerve stimulation; they are less effective when compared with ECT.

Target and Efficacy

In 1997, Mayberg et al hypothesised the first model for DBS on patients with depression based on positron emission tomography (PET) findings of subcallosal cingulate (SCC) hyperactivity in depression and decreasing metabolism in the same region following a variety of antidepressants treatment.[25] Subsequently, the group performed DBS targeting SCC with half of the patients achieving full or near-full remission after six months of stimulation. Following trial for DBS targeting SCC showed that chronic stimulation up to six months resulted in a response rate of 33% to 58%.[26]

Hints of another target for DBS, the VC/VS or nucleus accumbens (NAc), have been suggested when DBS was employed for OCD.[27] Depressive symptoms were noted to be improved after DBS for OCD. However, subsequent studies and trials have shown conflicting results. On the other hand, nucleus accumbens is known to play an important role in reward-seeking behaviour. Anhedonia is first to improve during NAc stimulation in TRD.[28] Acute return of depressive symptoms was seen upon discontinuation of stimulation, while reinitiation of stimulation resulted in the return of the antidepressant effects.

Medial forebrain bundle, the white matter tract connecting ventral tegmentum and nucleus accumbens, has also been targeted with a response rate of 87%.[29] Other targets include inferior thalamic peduncle, lateral habenular complex and rostral cingulate gyrus.

Mechanism

It is well known that serotonin plays an important role for its antidepressant effect.

Stimulation of the NAc has been associated with increased monoamine levels in rats corresponding to improvement in depressive- and/or anxiety-like behaviours. Mechanism of DBS for TRD may also involve upregulation of neurotrophic systems. Stimulation of the NAc and the ventral tegmental area has been associated with increased brain-derived neurotrophic factor (BDNF) levels in rats.

Potential of DBS in Depression

In general, DBS for treatment for TRD has achieved response rates of 30 to 50%. For patients with severe TRD failing different medications, psychotherapy and other noninvasive measures, findings of sustained remission and of re-emergence of severe symptoms when crossing from active to sham stimulation are encouraging. Mania, hypomania, psychosis, motor effects, and rarely suicides have been reported during these trials; otherwise, DBS in general is well tolerated.

Limitations remain. On literature review, there are conflicting results on the effectiveness of treatment, and there is no evidence as to which target site is the best for TRD or how to pick and choose the suitable target sites on patients with TRD. One also needs to address the ethical issues with regard to patient consent, as well as the choice of patients to receive TRD.[30]

OTHER PSYCHIATRIC DISORDERS

Limited cases have been reported for schizophrenia, post-traumatic stress disorder (PTSD), aggressive and self-injurious behaviour (SIB), addiction and substance abuse and anorexia nervosa (AN).

A few case reports described DBS for SIB associated with aggression or mutism targeting amygdala, posterior hypothalamic region, globus pallidus internus (GPi) and ventral capsule/ventral striatum (VC/VS). Mechanism of action and the exact role of DBS remain unclear due to limited evidence. Stimulation of amygdala may also play a part in patients with refractory PTSD.

Role of nucleus accumbens (NAc) and its circuit to the ventral tegmental area (VTA) has been studied in reward learning and repetitive behaviour. Case reports have shown that targeting NAc may help abstinence in heroin use, alcoholism and smoking. Furthermore, roles of NAc and VTA have also been studied in the treatment of schizophrenia.

Medical and cognitive behavioural therapy fail in 30% of patients with AN. DBS targeting subcallosal cingulate sulcus (SCC), nucleus accumbens (NAc) and ventral capsule/ ventral striatum(VC/VS) reported as case series suggests its role as a potential alternative for patients failing traditional treatment.

CONCLUSION

The field of deep brain stimulation is expanding, given its potential uses in various disease management and technical improvement. There are no effective alternatives for some of the diseases mentioned above. As such, deep brain stimulation remains the last resort in view of its recent technical advances and ongoing clinical trials. However, there is still a lack of evidence and a need for clinical researches to prove its efficacy and to overcome ethical concerns.

References

1. Boon P, Raedt R, de Herdt V, Wyckhuys T, Vonck K. Electrical stimulation for the treatment of epilepsy. Neurotherapeutics. 2009 Apr; 6(2):218-27.

2. Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia. 2010;51:899–908.
3. Velasco AL, Velasco F, Jiménez F, et al. Neuromodulation of the centromedian thalamic nuclei in the treatment of generalized seizures and the improvement of the quality of life in patients with Lennox–Gastaut syndrome. Epilepsia.2006 Jul;47(7):1203-12.
4. McLardy T, Mark V, Scoville W, Sweet W. Pathology in diffuse projection system preventing brainstem-electrode arousal from traumatic coma. Confin Neurol 1969; 31:219–225.
5. Sudhin A. Shah, Nicholas D. Schiff. Central thalamic deep brain stimulation for cognitive neuromodulation: a review of proposed mechanisms and investigational studies. Eur J Neurosci. 2010 Oct; 32(7): 1135–1144.
6. Schiff ND, Giacino JT, Kalmar K, Victor JD, Baker K, Gerber M, Fritz B, Eisenberg B, Biondi T, O'Connor J, Kobylarz EJ, Farris S, Machado A, McCagg C, Plum F, Fins JJ, Rezai AR.Behavioural improvements with thalamic stimulation after severe traumatic brain injury.Nature. 2007 Aug 2;448(7153):600-3.
7. Chudy D, Deletis V, Almahariq F, Marčinković P, Škrlin J, Paradžik V. Deep brain stimulation for the early treatment of the minimally conscious state and vegetative state: experience in 14 patients. J Neurosurg 2018 Apr;128(4):1189-1198.
8. Sotirios Posporelisa, Anthony S. Davida,b, Keyoumars Ashkanc. Deep Brain Stimulation of the Memory Circuit: Improving Cognition in Alzheimer's Disease. J Alzheimers Dis. 2018;64(2):337-347.
9. Laxton AW, Tang-Wai DF, McAndrews MP, Zumsteg D, Wennberg R, Keren R, Wherrett J, Naglie G, Hamani C, Smith GS, Lozano AM. A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. Ann Neurol 2010;68, 521-534.
10. Fontaine D, Deudon A, Lemaire JJ, Razzouk M, Viau P, Darcourt J, Robert P. Symptomatic treatment of memory decline in Alzheimer's disease by deep brain stimulation: A feasibility study. J Alzheimers Dis 2013; 34:315-323.
11. Tyagi H, Zrinzo L, Akram H, et al. A randomised controlled trial of deep brain stimulation in obsessive compulsive disorder: a comparison of ventral capsule/ventral striatum and subthalamic nucleus targets. J Neurol Neurosurg Psychiatry. 2017; 88(8):A8.2–A9
12. Kuhn J, Hardenacke K, Lenartz D, Gruendler T, Ullsperger M, Bartsch C, Mai JK, Zilles K, Bauer A, Matusch A, Schulz RJ, Noreik M, Buhrle CP, Maintz D, Woopen C, Haussermann P, Hellmich M, Klosterkotter J, Wiltfang J, Maarouf M, Freund HJ, Sturm V. Deep brain stimulation of the nucleus basalis of Meynert in Alzheimer's dementia. Mol Psychiatry. 2015; 20:353-360.
13. Hardenacke K, Hashemiyoon R, Visser-Vandewalle V, Zapf A, Freund HJ, Sturm V, Hellmich M, Kuhn J. Deep brain stimulation of the nucleus basalis of Meynert in Alzheimer's dementia: Potential predictors of cognitive change and results of a long-term follow-up in eight patients. Brain Stimul. 2016; 9:799-800.
14. Scharre DW, Weichart E, Nielson D, Zhang J, Agrawal P, Sederberg PB, Knopp MV, Rezai AR, Alzheimer's Disease Neuroimaging Initiative. Deep brain stimulation of frontal lobe networks to treat Alzheimer's disease. J Alzheimers Dis 2018; 62:621-633.
15. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci. 1986; 9:357–381.
16. McGovern RA, Sheth SA. Role of the dorsal anterior cingulate cortex in obsessive-compulsive disorder: converging evidence from cognitive neuroscience and psychiatric neurosurgery. J Neurosurg. 2017; 126(1):132–147.
17. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch Gen Psychiatry. 1989; 46(11):1006–1011
18. Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. Lancet. 1999; 354(9189):1526.
19. Luyten L, Hendrickx S, Raymaekers S, Gabriëls L, Nuttin B. Electrical stimulation in the bed nucleus of the stria terminalis alleviates severe obsessive- compulsive disorder. Mol Psychiatry. 2016; 21(9):1272–1280.
20. Goodman WK, Foote KD, Greenberg BD, et al. Deep brain stimulation for intractable obsessive compulsive disorder: pilot study using a blinded, stag- gered-onset design. Biol Psychiatry. 2010; 67(6):535–542.
21. Greenberg BD, Gabriels LA, Malone DA, Jr, et al. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. Mol Psychiatry. 2010; 15(1):64–79.
22. Mallet L, Polosan M, Jaafari N, et al. STOC Study Group. Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. N Engl J Med. 2008; 359 (20):2121–2134.
23. Tyagi H, Zrinzo L, Akram H, et al. A randomised controlled trial of deep brain stimulation in obsessive compulsive disorder: a comparison of ventral capsule/ventral striatum and subthalamic nucleus targets. J Neurol Neurosurg Psychiatry. 2017; 88(8):A8.2–A9.
24. Fava M. Diagnosis and definition of treatment-resistant depression. Biol Psy- chiatry. 2003; 53(8):649–659.
25. Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. J Neuropsychiatry Clín Neurosci. 1997; 9(3):471–481.
26. Mayberg HS, Lozano AM, Voon V, et al. Deep brain stimulation for treatment- resistant depression. Neuron. 2005; 45(5):651–660.
27. Malone DA, Jr. Use of deep brain stimulation in treatment-resistant depres- sion. Cleve Clin J Med. 2010; 77 Suppl 3:S77–S80.
28. Schlaepfer TE, Cohen MX, Frick C, et al. Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. Neuropsycho-pharmacology. 2008; 33(2):368–377.
29. Schlaepfer TE, Bewernick BH, Kayser S, Mädler B, Coenen VA. Rapid effects of deep brain stimulation for treatment-resistant major depression. Biol Psychiatry. 2013; 73(12):1204–1212.
30. Fisher CE, Dunn LB, Christopher PP, et al. The ethics of research on deep brain stimulation for depression: decisional capacity and therapeutic misconception. Ann N Y Acad Sci. 2012; 1265:69–79.

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Abbreviation list: CBZ=carbamazepine; VPA=Sodium valproate; TPM=Topiramate; OXC=Oxcarbazepine; LTG=Lamotrigine; LEV=Levetiracetam; QoL=Quality of life

References: 1. Hagemann A, et al. Epilepsy Res 2013;104:140–150. **2.** Keppra Prescribing Information ver.NCDS 06 **3.** Aldenkamp A, et al. Epileptic Disord. 2016;18(Suppl.1): S55-S67 **4.** López-Góngora Epileptic Disord 2008; 10 (4): 297-305 **5.** Schmidt D. BMJ 2014;348:g254 **6.** Zhu F, et al. Chin Med J 2015;128:3015–3022

Name of medicinal product: Keppra **Qualitative and quantitative composition:** *Tablets* 250 mg / 500 mg / 1000 mg; *Oral Solution* 100 mg/ml; *Concentrate for solution for infusion* 100 mg/ml **Indication:** As monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy OR as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy, myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy, primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy. **Dosage and Route of Administration:** Levetiracetam therapy can be initiated with either intravenous or oral administration. Conversion to or from oral to intravenous administration can be done directly without titration. The total daily dose and frequency of administration should be maintained. *Film-coated tablets* and *Oral solution* may be taken with or without food and the daily dose is administered in two equally divided doses. *Concentrate for solution for infusion* is for intravenous use only and the recommended dose must be diluted in at least 100 ml of a compatible diluent and administered intravenously as a 15-minute intravenous infusion. There is no experience with administration of intravenous levetiracetam for longer period than 4 days. Levetiracetam concentrate is an alternative for patients (adults and children from 4 years of age) when oral administration is temporarily not feasible **Adults** *Monotherapy* Adults and adolescents from 16 years of age Initial dose 250 mg twice daily, then increase to an initial therapeutic dose of 500 mg twice daily after 2 weeks. May increase by 250 mg twice daily every 2 weeks depending upon the clinical response. Max. dose 1500 mg twice daily. *Add-on therapy* Adults (≥18 years) and adolescents (12 to 17 years) weighing ≥50 kg Initial therapeutic dose 500 mg twice daily (can be started on the first day of treatment). May adjust by 500 mg twice daily every 2 – 4 weeks depending upon the clinical response. Max. dose 1500 mg twice daily. **Children** *Monotherapy* No data available. *Add-on therapy* Children aged from 4 years of age and adolescents weighing <50 kg Initial therapeutic dose 10 mg/kg twice daily. Depending upon the clinical response and tolerability, the dose can be increased up to 30 mg/kg twice daily. Dose changes should not exceed adjustments of 10 mg/kg twice daily every 2 weeks. Dose in children weighing ≥50 kg is the same as in adults. **Contraindications:** Hypersensitivity to the active substance or other pyrrolidone derivatives or any of the excipients. **Warnings and Precautions** *Discontinuation* It is recommended to withdraw *KEPPRA* gradually (e.g. in adults and adolescents weighing ≥50 kg: 500 mg decreases twice daily every 2 – 4 weeks; in children and adolescents weighing <50 kg: dose decrease should not exceed 10 mg/kg twice daily every 2 weeks. *Paediatric population* The tablet formulation is not adapted for use in children under the age of 6 years and initial treatment in children weighing <25 kg. Available data in children did not suggest impact on growth and puberty. However, long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children remain unknown. *Renal impairment* The administration of *KEPPRA* to patients with renal impairment (especially elderly ≥65 years) may require dose adjustment. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection. *Suicide* Suicide, suicide attempt and suicidal ideation have been reported in patients treated with anti-epileptic agents (including levetiracetam). A meta-analysis of randomized placebo-controlled trials of anti-epileptics medicinal products has shown a small increased risk of suicidal thoughts and behavior. The mechanism of this risk is not known. Therefore patients should be monitored for signs of depression and/or suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should any symptoms of depression and/or suicidal ideation or behavior emerge. *Excipients – oral solution* Keppra 100 mg/ml oral solution contains methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions. It also contains maltitol liquid; patients with rare hereditary problems of fructose intolerance should not take this medicinal product. *Excipients – concentrate for solution for infusion* This medicinal product contains 2.5 mmol (or 57 mg) sodium per maximum single dose (0.8 mmol [or 19mg] per vial). To be taken into consideration by patients on a controlled sodium diet. **Interactions:** Enzyme-inducing antiepileptic medicinal products; probenecid, NSAIDs, sulphonamides, methotrexate. **Pregnancy and Lactation:** *Fertility* No impact on fertility was detected in animal studies. No clinical data are available. The potential risk for humans is unknown. *Preganncy* Keppra is not recommended during pregnancy and in women of childbearing potential not using contraception unless clearly necessary. Studies in animals have shown reproductive toxicity. Physiological changes during pregnancy may affect levetiracetam concentration. Decreased in levetiracetam plasma concentrations has been observed during pregnancy. This decrease is more pronounced during the third trimester (up to 60% of baseline concentration before pregnancy). Appropriate clinical management of pregnant women treated with levetiracetam should be ensured. Discontinuation of antiepileptic treatments may result in exacerbation of the disease which could be harmful to the mother and the foetus. *Lactation* Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended. **Ability to perform tasks that require judgement, motor or cognitive skills:** Levetiracetam has minor or moderate influence on the ability to drive and use machines. Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, especially at the beginning of treatment or following a dose increase. Therefore, caution is recommended in those patients when performing skilled tasks, e.g. driving vehicles or operating machinery. Patients are advised not to drive or use machines until it is established that their ability to perform such activities is not affected. **Adverse Reactions:** Nasopharyngitis, anorexia, depression, hostility/aggression, anxiety, insomnia, nervousness/ irritability, somnolence, headache, convulsion, dizziness, tremor, balance disorder, lethargy, veretigo, cough, abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, rash, asthenia/fatigue. **Overdosage** Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with *Keppra* overdoses. After an acute overdose, the stomach may be emptied by gastric lavage or by induction of emesis. There is no specific antidote for levetiracetam. Treatment of an overdose will be symptomatic and may include haemodialysis. The dialyser extraction efficiency is 60% for levetiracetam and 74% for the primary metabolite. Please read the full prescribing information prior to administration. Full prescribing information is available on request from GlaxoSmithKline Ltd, 23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong. Abbreviated Prescribing Information based on PI version NCDS 06.

GlaxoSmithKline Limited
23 / F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong. Tel: (852) 3189 8989 Fax: (852) 3189 8931 hk.gsk.com

HKRX/LTM/0013/17a(1) (01/2021)
Date of preparation 22/02/2019

Keppra levetiracetam

MCHK CME Programme Self-assessment Questions

Please read the article entitled "Deep Brain Stimulation Beyond the Movement Disorders" by Dr Ben Chat-fong NG, Dr Cannon Xian-lun ZHU, Dr Danny Tat-ming CHAN & Dr Wayne Wai-sang POON and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 May 2020 Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. **Deep brain stimulation can only treat movement disorders.**
2. **Depression is a Food and Drug Administration (FDA)-approved indication for deep brain stimulation.**
3. **The anterior nucleus of the thalamus is commonly targeted in deep brain stimulation for drug-resistant epilepsy.**
4. **Wakefulness is preserved in patients with persistent vegetative state.**
5. **Deep brain stimulation may help to improve the consciousness in patients with persistent vegetative state or minimally conscious state.**
6. **The substantia nigra is targeted for deep brain stimulation in a patient with Alzheimer's disease.**
7. **Deep brain stimulation may be considered in patients with obsessive compulsive disorder failing one trial of selective serotonin reuptake inhibitors.**
8. **Obsessive compulsive disorder is a Food and Drug Administration (FDA)- approved indication for DBS.**
9. **Treatment-resistant depression is commonly defined as an episode of major depression that has not improved after at least two adequate trials of different classes of antidepressants.**
10. **Deep brain stimulation may play a role in the treatment of addiction and substance abuse.**

ANSWER SHEET FOR MAY 2020

Please return the completed answer sheet to the Federation Secretariat on or before 31 May 2020 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Deep Brain Stimulation Beyond the Movement Disorders

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1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Name (block letters):_____ HKMA No.: _____ CDSHK No.: _____

HKID No.: __ __ - __ __ __ __ X X (X) HKDU No.: _____ HKAM No.: _____

Contact Tel No.:_____ MCHK No. / DCHK No.: _____(must fill in)

Answers to April 2020 Issue

The Current Management of Psoriatic Arthritis – Early Diagnosis, Monitoring of Disease Severity and Cutting-Edge Therapies

1. F 2. T 3. T 4. F 5. F 6. T 7. F 8. T 9. F 10. T

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OPTUNE® + TMZ[2]

5%
TMZ alone[2]

Abbreviations: GBM=glioblastoma multiforme; TMZ=temozolomide

References: 1. Data on file. Novocure. Last updated January 2019. **2.** Stupp, R. *et al.* JAMA 318, 2306–2316 (2017).

Indications for Use Optune Treatment Kit is intended for the treatment of patients with newly diagnosed GBM and for the treatment of patients with recurrent GBM. **Newly diagnosed GBM** NovoTTF-200A (Optune™) Treatment Kit is intended for the treatment of patients with newly diagnosed GBM, after surgery and radiotherapy with adjuvant Temozolomide, concomitant to maintenance Temozolomide. The treatment is intended for adult patients, 18 years of age or older, and should be started more than 4 weeks after surgery and radiation therapy with adjuvant Temozolomide. Treatment may be given together with maintenance Temozolomide (according to the prescribing information in the Temozolomide package insert) and after maintenance Temozolomide is stopped. **Recurrent GBM** NovoTTF-200A (Optune™) Treatment Kit is intended for the treatment of patients with recurrent GBM who have progressed after surgery, radiotherapy and Temozolomide treatment for their primary disease. The treatment is intended for adult patients, 18 years of age or older, and should be started more than 4 weeks after the latest surgery, radiation therapy or chemotherapy. **Contraindications** Do not use Optune Treatment Kit if you are pregnant, think you might be pregnant, or are trying to get pregnant. If you are a woman who is able to get pregnant, you must use birth control when using the device. Optune Treatment Kit was not tested in pregnant women. Do not use Optune Treatment Kit if you have significant additional neurological disease (primary seizure disorder, dementia, Progressive degenerative neurological disorder, Meningitis or encephalitis, Hydrocephalus associated with increased intracranial pressure) Do not use Optune Treatment Kit if you are known to be sensitive to conductive hydrogels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes. In this case, skin contact with the gel used with Optune Treatment Kit may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure. Do not use Optune if you have an active implanted medical device, a skull defect (such as, missing bone with no replacement) or bullet fragments. Examples of active electronic devices include deep brain stimulators, spinal cord stimulators, vagus nerve stimulators, pacemakers and defibrillators. Use of Optune together with implanted electronic devices has not been tested and may lead to malfunctioning of the implanted device. Use of Optune together with skull defects or bullet fragments has not been tested and may possibly lead to tissue damage or render Optune ineffective. Ref: EU IFU Document number QSD-EUUM-001-EN (Rev 04)

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HK-OPT-201910-02

Latest Developments in Interventional Neuroradiology

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INTRODUCTION

In the last three decades, we have been witnessing a rapid expansion of minimally invasive surgery. Endovascular neuro-intervention for cerebrovascular diseases is definitely one of the most representative examples. With new devices and techniques expanding the scope of diseases that can be treated, the volume of these procedures has increased substantially. The objective of this review article is to introduce these latest developments in the endovascular treatment of acute ischemic stroke, intracranial arterial stenosis, cerebral aneurysms, cerebral vascular malformations and other rarer but important treatable conditions.

As the treatment modalities described in this article are rapidly changing and multiple clinical trials are ongoing, this document only serves to give a summary of the latest development in the field of interventional neuroradiology and not as clinical guidelines.

INTRA-ARTERIAL MECHANICAL THROMBECTOMY (IAT) FOR ACUTE STROKE THERAPY

The use of intravenous recombinant human tissue plasminogen activator (r-tPA) for acute ischaemic stroke (AIS) within 3 hours from symptom onset became the standard therapy upon the release of the landmark National Institute of Neurological Disorders and Stroke (NINDS) trial in thrombolysis therapy in 1995[1]. In 2008, the ECASS III (European Cooperative Acute Stroke Study III) further expanded the treatment window for intravenous r-tPA to 4.5 hours[2]. Unfortunately, not all patients benefit from IV r-tPA, such as those outside the treatment time window or having large arterial occlusion.

Since then, more effective means to re-open occluded brain vessels became the target of further clinical researches. It was not until 2015, when five randomised clinical trials provided Level 1A evidence for the benefit of endovascular treatment over intravenous r-tPA in large vessel occlusion stroke. **MR CLEAN** (Multicenter Randomised Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke) was the first multi-centre RCT to establish the superiority of adjunctive endovascular treatment over intravenous r-tPA/medical therapy alone[3]. It is a multi-centre study conducted in Netherlands. Five hundred patients with AIS were randomized. Inclusion criteria of National Institute of Health Stroke Score (NIHSS) score ≥ 2 (median NIHSS score, 17), < 6 hours from symptom onset and an anterior circulation large vessel occlusion (ICA, MCA, ACA) confirmed by CTA/MRA imaging. 58.7% received IA therapy demonstrated recanalisation of the vessels. Despite such modest endovascular recanalisation rates plus nearly 3-hour delays after intravenous r-tPA treatment, the primary outcome was reported in favour of interventional therapy with an adjusted OR of 1.67 (95% CI, 1.21–2.30) and 13.5% (95% CI, 5.9–21.2) absolute difference in functional independence (32.6% versus 19.1% with Modified Rankin Score scores of 0 – 2 at 90 days). Within the same year, four other clinical trials[4-7] confirmed the same findings, supporting the benefit of intra-arterial mechanical therapy. In 2016, FDA approved the marketing of the Solitaire device as an initial therapy for AIS for patients with a proximal anterior circulation large vessel occlusion, to reduce paralysis, speech difficulties and other stroke-related disabilities (Fig. 1).

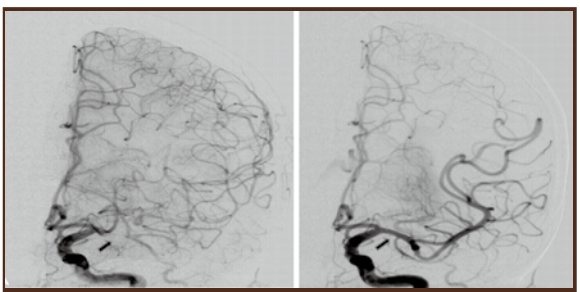

Fig. 1a Cerebral digital subtraction angiography (DSA) showing occluded left middle cerebral artery (arrow). Recanalised left MCA after intra-arterial mechanical thrombectomy. (Photo from Personal Collection)

Fig. 1b Intra-operative photo showing Solitaire stent successful retrieval of thrombus. (Photo from Personal Collection)

A meta-analysis study was conducted by the **HERMES** collaboration (Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials)[8]. With advanced imaging, either MR Diffusion Weighted Image (DWI) – Perfusion Weighted Image (PWI) or CT Perfusion (CTP) imaging to select patients with adequate cerebrovascular reserve outside the treatment window of 6 hours from stroke onset, these patients continued to benefit from endovascular treatment. This finding was further

supported by the **DAWN** trial (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) and **DEFUSE-3** trial (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) [9,10].

The technical goal of the thrombectomy procedure should be a *Thrombolysis In Cerebral infarction (TICI)* grade 2b/3 angiographic result to maximise the probability of a good functional clinical outcome.
- *Grade 2B: complete filling of all of the expected vascular territory is visualised but the filling is slower than normal*
- *Grade 3: complete perfusion*

The **DAWN** study proved that among patients with acute stroke who had last been well from 6 to 24 hours and who had a mismatch between clinical deficit and infarct core, based on advance imaging findings, outcomes for disability at 90 days were better with thrombectomy.

In summary, patients should receive endovascular therapy with a stent retriever/aspiration device if they meet all the following criteria:

(1) *Pre- stroke mRS score of 0-1*
(2) *occlusion of the ICA or proximal MCA (M1)*
(3) *age ≥18 years*
(4) *NIHSS score of ≥6*
(5) *ASPECTS score of ≥6*
(6) *groin puncture within 6 hours of symptom onset, or from 6-24 hours if salvageable penumbra was demonstrated by perfusion imaging and the infarct core was small*

ENDOVASCULAR TREATMENT OF CEREBRAL ANEURYSMS

Even though cerebral aneurysms affect a relatively small number of people each year, the poor outcome associated with subarachnoid haemorrhage can be devastating. The prevalence of un-ruptured intracranial aneurysm is estimated to be up to 2% in an analysis of brain MR images[11]. Such un-ruptured intracranial aneurysm is getting more commonly detected nowadays as brain MRI and MR angiography are widely available.

Natural History

ISUIA (International Study of Unruptured Intracranial Aneurysms) is the first large-scale study to assess the natural history of cerebral aneurysm[12]. It is a retrospective review of the natural history of 1,449 patients with 1,937 unruptured aneurysms selected for conservative management. Among patients with no history of SAH, the rupture risk was 0.05%/year for aneurysms < 10 mm, and ≈ 1%/year for larger aneurysms. Larger aneurysm size and location in the posterior circulation were adverse risk factors for rupture. For those with a prior history of subarachnoid haemorrhage (SAH) from a different aneurysm, the rupture risk was 0.5%/year for aneurysms < 10 mm and ≈ 1%/year for larger aneurysms.

The 2012 **UCAS** study conducted in Japan is a prospective cohort study of 5,720 patients with 6,697 unruptured cerebral aneurysms[13]. The overall annual risk of rupture was found to be 0.95%/year. Size of the lesion, location, and presence of a daughter sac were risk factors for rupture. The 5-year risk of rupture for small aneurysms (< 5 mm) was 1.7%.

As expected, these studies are prone to selection bias because the group of aneurysms reserved for observation are probably less likely to haemorrhage. Those deemed to be at higher risk would have been treated rather than recruited into the observational group. It is therefore likely that the observed haemorrhage rates in these studies are underestimated.

Endovascular Interventional of Cerebral Aneurysms

Before the era of endovascular intervention, microsurgery with clipping was the standard treatment for cerebral aneurysms. The array of endovascular treatment options for intracranial aneurysms has evolved dramatically over the past three decades. From the introduction of the Guglielmi Detachable Coil (GDC) in 1990[14] to the latest development of flow diverters, technological advancements allow safer and effective treatment options for patients with cerebral aneurysms, for both ruptured and unruptured.

Ruptured Cerebral Aneurysms

Subarachnoid haemorrhage from ruptured cerebral aneurysm carries significant morbidity and mortality for the patients. The 2005 **ISAT** (International Subarachnoid Aneurysm Trial) was an international multicentre randomised clinical trial comparing ruptured cerebral aneurysm treated by surgical clipping versus endovascular coiling[15]. The primary outcome was death or dependence at 1-year. The primary outcome happened in 250/1,063 (23.5%) of patients allocated to endovascular treatment; compared to 326/1,055 (30.9%) in patients allocated to microsurgery. This difference was translated into an absolute risk reduction of 7.4% (95% CI 3.6-11.2, p=0.0001). After this non-inferiority study, endovascular coiling is firmly established as a standard option to treat both ruptured and non-ruptured aneurysms. Long-term reconstitution of coiled aneurysms remains a concern though. Upon 9-year follow up, the risk of rebleeding from the treated aneurysm was higher with coiling than clipping, but the risks were very small (10 in the coiling group with 8,447 person-years of follow-up versus 3 in the clipping group with 8,177 person-years follow-up), equivalent to a rebleeding risk of 0.1%/y in the coiled patients and 0.03%/y in the clipped patients[16].

Built on the basis of endovascular coiling, there have been numerous studies to use adjunctive devices, such as balloon-assisted technique, stent-assisted technique or neck–bridging devices to enable a more stable coil mass as well as a better, safer and more permanent coil packing of cerebral aneurysms while preserving the blood flow of the main arterial trunks and other side branches[17]. (Fig 2)

Fig. 2a Drawing showing an inflated balloon during deployment of coils into the aneurysm sac, preserving the patency of the parent artery. When coiling is completed, the balloon will be deflated. (Excerpted from Laurent Pierot, et al. Endovascular Treatment of Intracranial Aneurysms. Stroke, 44, Issue 7, July 2013, P.2046-2054)

Fig. 2b Photo showing stent assisted coiling of cerebral aneurysm model. The stent strut prevents the coil from protruding into the parent trunk. (Excerpted from Fiorella D, Kelly ME, Turner RD, Lylyk P. Endovascular treatment of cerebral aneurysms. Endovascular Today. 2008; June:53-65.)

Unruptured Cerebral Aneurysms

The management of incidental unruptured cerebral aneurysms is more controversial. Despite the widespread array of endovascular treatment options, the question of whether one should observe or treat an unruptured, asymptomatic aneurysm remains unanswered by clinical trials.

A systematic review of a pooled analysis of individual patient data from 8,382 participants in six prospective cohort studies looking at subarachnoid haemorrhage as the outcome was performed in 2013[21]. The mean observed 1-year risk of aneurysm rupture was 1.4% (95% CI 1.1–1.6), and the 5-year risk was 3.4% (2.9–4.0). Predictors for a higher risk of SAH were age, hypertension, history of SAH, aneurysm size, aneurysm location, and geographical region (PHASES score). In comparison to populations from North America and European countries other than Finland, Finnish people had a 3.6-times increased risk of aneurysm rupture and Japanese people a 2.8-times increased risk. These factors should be considered individually when deciding the management direction, and the physicians should balance the estimated rupture risk with the risk of intervention in counseling the patients regarding treatment decision.

Flow Diverters

The most important technological innovation since the detachable coil is flow diverter[18]. A flow diverter is an endoluminal stent-like construct designed to re-construct the diseased parent artery across from where the aneurysm arises (Fig. 3). The stent strut is manufactured such that blood flow into the aneurysm sac was disrupted and allowed endothelial cells to grow across the stent interstices and finally seal the aneurysm but preserving the flow to the side branches. Several large series of flow diversion have shown remarkable results for the treatment of large or giant cerebral aneurysms that are prone to recur with conventional endovascular coiling[18]. However, the major criticism for many studies is the risk of thromboembolism, particularly at the side branches which will be covered by the stent strut. Therefore, adequate antiplatelet therapy is essential and this is the limitation which confines the use of flow diverter predominantly for unruptured cerebral aneurysms[19].

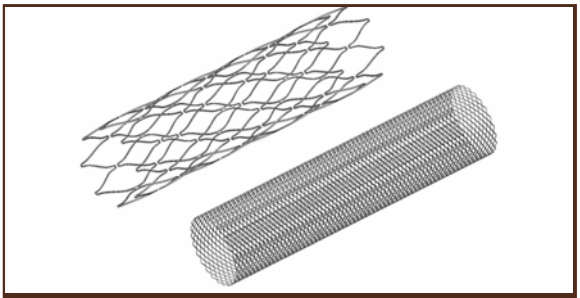

Fig. 3aGeometry of Neuroform EZ stent (upper left) and Pipeline device (lower right). Note that the porosity of the Pipeline flow diversion stent is much higher than that of the Neuroform EZ neck bridging stent. (Excerpted from Yasuhiro Shobayashi, et al. Intra-aneurysmal hemodynamic alterations by a self-expandable intracranial stent and flow diversion stent: high intra-aneurysmal pressure remains regardless of flow velocity reduction. J NeuroIntervent Surg 2013;5:iii38–iii42)

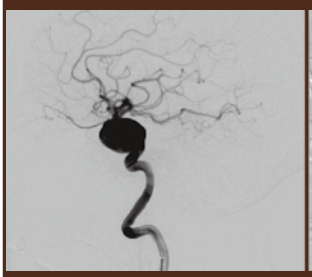

Fig. 3b Cerebral angiography showing a giant non-ruptured left internal carotid artery (ICA) aneurysm before treatment by a flow diverter (Photo from Personal Collection)

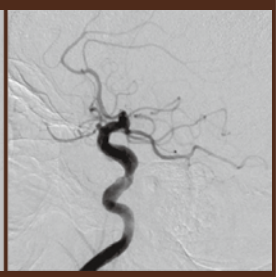

Fig. 3c 18-month follow up angiography after flow diverter showing near complete disappearance of the left ICA aneurysm. (Photo from Personal Collection)

In one local prospective non-randomised multi-centre study conducted in Hong Kong, 143 patients with 178 unruptured saccular or fusiform aneurysms or recurrent aneurysms after previous treatment were included and observed angiographically for up to 18 months and clinically for up to 3 years[20]. Angiographic results at 18 months revealed a complete aneurysm occlusion rate of 84% (49 of 58; 95% CI: 72.1%, 92.2%), with no case of parent artery occlusion. There were 5 (3.5%) cases of peri-procedural death or major stroke (modified Rankin Scale [mRS] > 3) (95% confidence interval [CI]: 1.3%, 8.4%), including two post-treatment delayed ruptures, two intracerebral hemorrhages, and one thromboembolism. Five (3.5%) patients had minor neurologic complications within 30 days (mRS = 1) (95% CI: 1.3%, 8.4%), including transient ischemic attack (n = 2), small cerebral infarction (n = 2), and cranial nerve palsy (n = 1). Overall, flow diverter placement is considered a reasonably safe and effective treatment for intracranial aneurysms.

New Devices for Cerebral Aneurysm

There has been ongoing innovation in devices for

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Date	Topics	Speakers
5 June, 2020	New algorithms in prenatal diagnosis and interpretation of reports	Dr. Wing-cheong LEUNG Consultant Obstetrician & Chief-of-service, Department of O&G, Kwong Wah Hospital
12 June, 2020	Ultrasound examination of normal and abnormal fetal heart	Dr. Ben Chong-Pun CHAN Private Obstetrician
19 June, 2020	Ultrasonography of twin pregnancies and complications	Dr. Kwok-Yin LEUNG President, Hong Kong Society for Ultrasound in Medicine
26 June, 2020	Ultrasound diagnosis of brain and spine anomalies	Dr. Ka Wang CHEUNG Consultant, Obstetrics & Gynaecology, Queen Mary Hospital
3 July, 2020	Ultrasound diagnosis and counseling of craniofacial anomalies	Dr. Meliza Choi-wah KONG Consultant, Obstetrics & Gynaecology, United Christian Hospital
10 July, 2020	A prenatal diagnostic approach to skeletal dysplasia	Dr. Anita Sik-yau KAN Consultant, Obstetrics & Gynaecology, Queen Mary Hospital

Date : 5, 12, 19, 26 June & 3, 10 July, 2020 (Every Friday)
Time : 7:00 p.m. – 8:30 p.m.
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Language Media : Cantonese (Supplemented with English)
Course Fee : HK$1,000 (6 sessions)
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treating difficult cerebral aneurysms. The newer generation of flow diverters targeting at small profile, better deliverability and surface modification to reduce thrombogenicity of the stent. Early experience has been promising which allows aneurysms in smaller arteries or more distal circulation to be treated with flow diverters, though long-term clinical efficacy and safety remain to be proven.

Preliminary results in small case series demonstrated the feasibility of endosaccular mesh devices or modified stent devices targeted for wide-necked bifurcation aneurysms (Fig. 4)[22-24]. Such devices are likely to improve the safety and efficacy for difficult-to-treat broad-necked aneurysms in the future. Readers are encouraged to keep track of these latest development in clinical studies.

Fig. 4a Drawing showing an endosaccular Woven EndoBridge (WEB) device deployed inside an aneurysm sac. (Excerpted from Jiang B,et al.Stroke and Vascular Neurology. 2016;1:e000027.)

Fig. 4b A drawing showing a Lunar Aneurysm embolisation device is deployed inside the aneurysm sac, preserving the arterial branches. (Excerpted from Kwon SC, et al. Preliminary Results of the Luna Aneurysm Embolisation System in a Rabbit Model: A New Intrasaccular Aneurysm Occlusion Device. AJNR 32 Mar 2011. P604-606)

Fig. 4c Photo showing the Medina Coiling System for aneurysm embolisation. The device was placed inside an aneurysm sac to induce thrombosis leading to occlusion of the aneurysm. (Excerpted from Aguilar Perez M,et al..J NeuroIntervent Surg 2017;9:77–87.)

ENDOVASCULAR TREATMENT OF INTRACRANIAL ATHEROSCLEROTIC STENOSIS

The management of intracranial atherosclerotic stenosis is not as straight forward as the well-established treatment of extracranial carotid artery stenosis. Firstly, we have to study the natural history of ICAS before further discussion of the management options. For stroke patients with significant intracranial arterial disease, the recurrent stroke rate is estimated to be 10-22% in the first year[25]. Hypertension, hyperlipidemia, type II diabetes mellitus and metabolic syndrome are associated risk factors. Balloon angioplasty and stenting, employing the same principle as extracranial disease, is a potential modality in addition to medical therapy. (Fig. 5) The **SAMMPRIS** trial compared aggressive medical therapy and percutaneous angioplasty plus stenting in patients with intracranial atherosclerotic 70-99% stenosis presenting within 30 days of a related stroke or TIA[26]. The trial was stopped after enrollment of 451 patients in April 2011, when a higher 30-day rate of stroke and death was present in the percutaneous angioplasty and stenting group compared with the aggressive medical therapy group (14.7% versus 5.8%; P=0.002). The **VISSIT** trial was another international multicenter clinical trial that compared balloon-expandable stents and medical therapy in patients with 70-99% symptomatic intracranial atherosclerotic disease. The study was halted, and analysis showed futility after 112 patients of a planned sample size of 250 were enrolled[27].

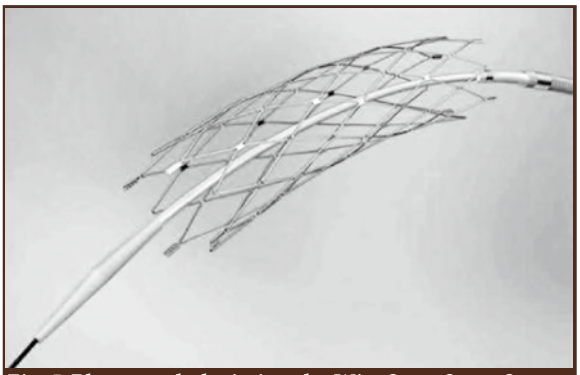

Fig. 5 Photograph depicting the WingSpan Stent System when deployed. (Excerpted from Kivilcim Yavuz, et al. Wingspan Stent System in the endovascular treatment of intracranial aneurysms: Clinical experience with midterm follow-up results. J Neurosurg 109 445-453, 2008)

In 2005, FDA issued a report narrowing the Humanitarian Device Exemption criteria for Wingspan stent which and limited its use to patients between 22 and 80 years of age who meet all of the following conditions: (1) The patient has had two strokes despite aggressive medical management; (2) the most recent stroke occurred > 7 days before the planned treatment with Wingspan; (3) there is 70% to 99% stenosis caused by intracranial atherosclerosis related to the recurrent strokes; and (4) the patient made a good recovery from the previous stroke with mRS score of ≤ 3 before Wingspan treatment. Furthermore, Wingspan should not be used for the treatment of stroke with onset of symptoms within ≤ 7 days of treatment or treatment of TIAs. If these selection criteria are strictly followed, as in the recent **WEAVE** study, the safety profile for intracranial stenting is much improved with only 2.6% 30-day and 8.5% one-year stroke or death rate.[28]

The China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis (**CASSISS**) trial is an ongoing, government-funded, prospective, multicenter trial. It recruits patients with recent TIA or stroke caused by 70-99% stenosis of a major intracranial artery[29]. The randomised phase started on Mar 2014 with a total of 380 patients recruited (1:1) to best medical therapy alone or medical therapy plus stenting in eight sites in China. Recruitment was completed in November 2016. Patients will be followed for at least three years. The trial is scheduled to complete in 2019. At the time of writing, the result is not released yet.

Recommendations

ICAS can cause stroke by either critical hypoperfusion, artery-to-artery emboli, or perforator occlusion. While medical therapy may be most effective for the latter two, those with critical stenosis causing hypoperfusion may benefit from angioplasty or stenting. Hence, proper patient selection and thorough analysis of the angiogram and ICAS lesion configuration is essential to ensure efficacy and safety.

For patients with mild to moderate intracranial arterial stenosis (< 70%), optimal medical therapy which includes aspirin, clopidogrel for 90 days, maintenance of systolic BP < 140 mmHg, statin therapy and aggressive risk factor modification are recommended. For patients with severe stenosis (70%–99%) of a major intracranial artery who have progressive symptoms and perfusion deficit; recurrent TIA; recurrent stroke despite best medical therapy; achievement of systolic BP < 140 mmHg and high-intensity statin therapy, angioplasty alone, or placement of a Wingspan stent may be warranted[30].

ENDOVASCULAR TREATMENT OF CEREBRAL ARTERIOVENOUS MALFORMATION (AVM)

Brain AVM is a relative rare disease. Patients usually present with seizure or acute bleeding. The AVM detection rate is about 1.3 per 100 000 person-years. A recent meta-analysis of the natural history in the absence of treatment showed an annual risk of recurrent haemorrhage of 4.8%[31]. The treatment of AVMs can be broadly classified into 4 options: observation, surgical resection, embolisation and radiosurgery. For a patient who has an incidental brain AVM, the first conundrum is whether to pursue conservative management or intervention.

The indication for embolisation treatment of AVM is among the most controversial topics in management of AVM. It can be used as a stand-alone treatment or in combination with other treatment modalities such as radiosurgery, or as a pre-operative intervention to minimise blood loss during surgery.

The ability to eradicate AVMs with endovascular embolisation alone has been improved with the introduction of the liquid embolic agent such as ethyl vinyl alcohol copolymer (Onyx, ethylene-vinyl copolymer; Medtronic, Inc). **Onyx®** is a non-adhesive liquid embolic agent comprised of EVOH (ethylene vinyl alcohol) copolymer dissolved in DMSO (dimethyl sulfoxide), and suspended micronised tantalum powder to provide a radio-opaque medium for visualisation under fluoroscopy. The development of detachable-tip microcatheters, which may mitigate the risks of catheter adhesion and withdrawal, may facilitate more thorough embolisation. With these materials, curative treatment with embolisation alone may be achieved in over 50% under expert hands, but the potential risk is also substantial with a 9.7% haemorrhage rate and 24.1% complication rate.[32]

ARUBA trial (A Randomised Trial of Unruptured Brain Arteriovenous Malformations) was designed to study the benefits of conservative management versus intervention in unruptured AVMs[33]. The primary endpoint was the composite measure of death from any cause or any stroke. The secondary analysis was overall functional status and quality of life at a minimum of 5 years from randomisation. An interim analysis led to discontinuation of the study due to excessive morbidity in the treatment arm as compared with the conservatively treated cohort. A total of 223 patients had been enrolled in the trial, with a mean follow-up of approximately 33.3 months. The primary outcome was seen in 11 (10.1%) of the 109 patients assigned to the medical group and in 35 patients (30.7%) of the 114 patients assigned to the intervention group. The result is disappointing to the interventionists as the conservative group has a lower incidence of stroke or death. The study was questioned, however, for the fact that the follow-up duration is short with a relatively small number of patients. Besides, even prior to commencement of enrollment, the design of the ARUBA study had been heavily criticised, particularly in regards to the proposed 5-year follow-up period, which many argued would unfairly detect all procedure-related complications but would be too short to detect the potential long-term benefits of prophylactic intervention.

Preoperative embolisation constitutes the most common application for endovascular treatment for brain AVM (Fig. 6). Another indication for endovascular treatment is as an adjunct to surgery or radiosurgery. In this scenario, embolisation can be used either to diminish the size of a brain AVM or to occlude high-risk features such as nidal and peri-nidal aneurysms before definitive treatment of the remaining portion of an AVM. Finally, embolisation has been used as a palliative treatment for refractory AVM in which excessive blood flow to the AVM is reduced by embolization of the feeding arteries and alleviate vascular steal symptoms of the surrounding brain parenchyma.

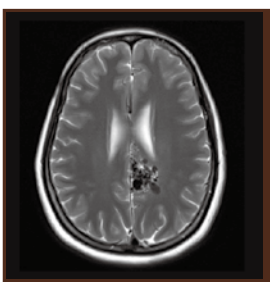

Fig. 6a T2 MRI brain image showing a AVM at the left posterior cingulate gyrus. (Photo from Personal Collection)

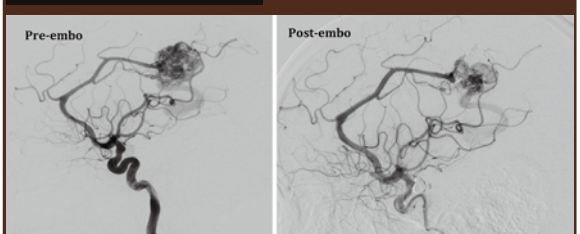

Fig. 6b Pre and Post embolisation cerebral angiogram showing decreased blood flow to the left cingulate gyrus AVM. (Photo from Personal Collection)

ENDOVASCULAR TREATMENT OF CEREBRAL VENOUS THROMBOSIS

Cerebral venous thrombosis (CVT) is an uncommon disease which accounts for 1% of all stroke. CVT is usually associated with risk factors such as congenital pro-thrombotic state, venous stasis, infection, trauma or oral contraceptive pills usage. Patients with CVT should be treated with systemic anticoagulation as first-line therapy. In patients who are at high risk for deterioration (e.g. severely depressed mental status, coma, major dural venous sinus thrombosis at presentation; those with neurological deterioration or increasing intracranial pressure despite systemic anticoagulation) the use of endovascular techniques, including direct intra-sinus thrombolysis or mechanical thrombectomy, may be considered to recanalise the occluded venous sinuses (Fig. 7).[34]

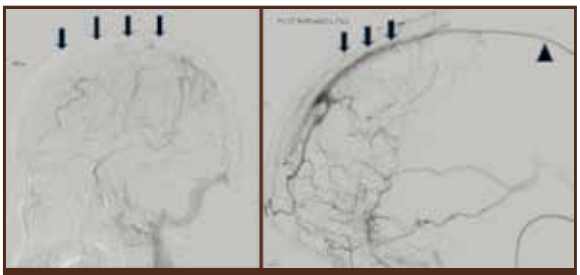

Fig. 7a Cerebral DSA venogram showing evidence of sinus occlusion at the anterior and middle third (black arrow) of the superior sagittal sinus. (Photo from Personal Collection)

Fig. 7b Post-thrombectomy venogram showed partial recanalisation of the anterior one-third of superior sagittal sinus (black arrow). Micro-catheter inside the sinus (arrowhead) (Photo from Personal Collection)

A retrospective study comparing intra-sinus thrombolytic infusion with mechanical thrombectomy (with or without thrombolytic) in 63 patients revealed that patients with more severe deficits were more likely to be treated with mechanical thrombectomy but that no difference in clinical response could be demonstrated[35]. Full recanalisation was achieved in 50% of patients, and full or partial recanalisation was achieved in 91%.

ENDOVASCULAR STENTING OF DURAL VENOUS SINUS FOR IDIOPATHIC INTRACRANICAL HYPERTENSION

Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri or benign intracranial hypertension, is a disorder with elevated intracranial pressure in the absence of a structural lesion. The primary medical treatments for IIH include weight loss, acetazolamide (reduce cerebrospinal fluid production), diuretics and lumbar punctures. CSF shunt is also a definitive therapy for intractable patients who fail medical therapy.

In certain patients who have transverse sinus stenosis contributing to the raised cerebral venous pressure, venous angioplasty +/- stenting (Fig. 8) can be an effective option. The evidence, however, is limited to cohort studies at the moment. The indications for endovascular treatment include failure of medical therapy, worsening of visual or neurological conditions, and venous pressure gradient of > 10 mmHg across the stenosis. Those with debilitating pulsatile tinnitus secondary to venous sinus flow turbulence may also benefit. Stenting is typically performed with self-expanding stents. A recent meta-analysis showed that the venous sinus stenting reduce headache, improve vision and resolution of papilledema of 83%, 78%, and 97%, respectively[36,37].

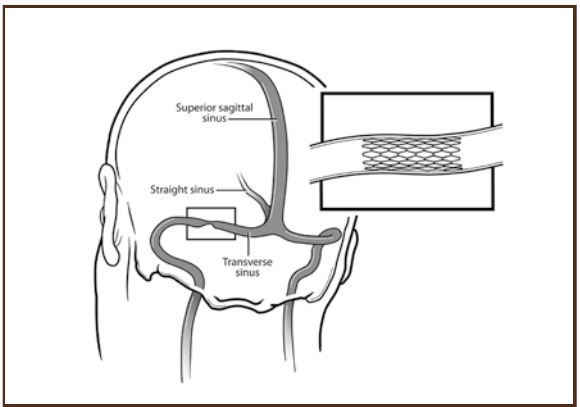

Fig. 8 Drawing showing a venous stenosis at the left transverse sinus. Stenting with angioplasty relieve the stenosis and normalise the elevated venous pressure. (Excerpted from Justin M. Cappuzzo, et al. Transverse venous stenting for the treatment of idiopathic intracranial hypertension, or pseudotumor cerebri. Neurosurg Focus 45 (1):E11, 2018)

SUMMARY

We have summarised the latest advancements in the field of Interventional Neuroradiology. The major breakthrough in the five years is no doubt the Intra-arterial Mechanical Thrombectomy for acute stroke therapy. It has been the standard of care in most of the developed countries. At the time of preparing this article, there have been numerous research studies on-going to further push the boundary of this field.

In Hong Kong, interventional neuroradiological services are provided by interventionists from neuroradiology, neurosurgery and neurology background, in both private and public sectors. They work harmoniously as a team. We believe with their concerted efforts, patients are going to receive the best possible care.

References

1. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581–1587.
2. Hacke W, et al. ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359:1317–1329.
3. Olvert A. Berkhemer, et. al. A Randomized Trial of Intra-arterial Treatment for Acute Ischemic Stroke. N Engl J Med. 2015; 372:11-20
4. Goyal M, et. al. ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015; 372: 1019–1030.
5. Campbell BC, et. al.; EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372:1009–1018.

6. Saver JL, et. al.; SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015;372:2285–2295.
7. Jovin TG, et. al.; REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372:2296–2306.
8. Goyal M, et. al. ERMES Collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomized trials. Lancet. 2016;387:1723–1731
9. Raul G. Nogueira, et al. The DAWN Trial Investigators. N Engl J Med. 2018; 378:11-21.
10. ClinicalTrials.gov. Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE 3). https://clinicaltrials.gov/ct2/show/NCT02586415. Accessed July 20, 2017
11. Vernooij MW, et. al.; Incidental findings on brain MRI in the general population. N Engl J Med. 2007; 357:1821–1828
12. Wiebers DO, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet. 2003 Jul 12; 362(9378): 103-10.
13. Morita A, et al. Kirino T, Hashi K, Aoki N, Fukuhara S, Hashimoto N, Nakayama T, Sakai M, Teramoto A, Tominari S, Yoshimoto T; UCAS Japan Investigators. The natural course of unruptured cerebral aneurysms in a Japanese cohort. N Engl J Med. 2012;366:2474–2482.
14. Guglielmi G, Vinuela F, Sepetka I, Macellari V. Electrothrombosis of saccular aneurysms via endovascular approach, part 1: electrochemical basis, technique, and experimental results. J Neurosurg. 1991;75:1–7.
15. Molyneux A, Kerr R, Stratton I, Sandercock P, Clarke M, Shrimpton J, Holman R; International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomized trial. Lancet. 2002;360: 1267–1274.
16. Molyneux AJ, Kerr RS, Birks J, Ramzi N, Yarnold J, Sneade M, Rischmiller J; ISAT Collaborators. Risk of recurrent subarachnoid haemorrhage, death, or dependence and standardized mortality ratios after clipping or coiling of an intracranial aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): long-term follow-up. Lancet Neurol. 2009;8:427–433.
17. Spelle L, Piotin M, Blanc R, Moret J. Remodeling techniques in the treatment of intracranial aneurysms: indications, limits and non-indications. Interv Neuroradiol. 2008;14(suppl 1):52–59.
18. Nelson PK, Lylyk P, Szikora I, Wetzel SG, Wanke I, Fiorella D. The Pipeline Embolization Device for the intracranial treatment of aneurysms trial. AJNR Am J Neuroradiol. 2011;32:34–40.
19. Raymond J, Gentric JC, Darsaut TE, Iancu D, Chagnon M, Weill A, Roy D. Flow diversion in the treatment of aneurysms: a randomized care trial and registry. J Neurosurg. 2017;127:454–462.
20. Simon Chun-Ho Yu, et al. Intracranial Aneurysms: Midterm Outcome of Pipeline Embolization Device—A Prospective Study in 143 Patients with 178 Aneurysms. Radiology: Volume 265: Number 3—December 2012
21. Greving JP, Wermer MJ, Brown RD Jr, Morita A, Juvela S, Yonekura M, Ishibashi T, Torner JC, Nakayama T, Rinkel GJ, Algra A. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. Lancet Neurol. 2014;13:59–66.
22. Klisch J, Sychra V, Strasilla C, Liebig T, Fiorella D. The Woven EndoBridge cerebral aneurysm embolization device (WEB II): initial clinical experience. Neuroradiology. 2011;53:599–607.
23. Kwon SC, Ding YH, Dai D, Kadirvel R, Lewis DA, Kallmes DF. Preliminary results of the Luna aneurysm embolization system in a rabbit model: a new intrasaccular aneurysm occlusion device. AJNR Am J Neuroradiol. 2011;32:602–606.
24. Turk AS, Maia O, Ferreira CC, Freitas D, Mocco J, Hanel R. Periprocedural safety of aneurysm embolization with the Medina Coil System: the early human experience. J Neurointerv Surg. 2016;8:168–172.
25. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, Levine SR, Chaturvedi S, Kasner SE, Benesch CG, Sila CA, Jovin TG, Romano JG; Warfarin-Aspirin Symptomatic Intracranial Disease Trial Investigators. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med. 2005;352:1305–1316.
26. Wojak JC, Dunlap DC, Hargrave KR, DeAlvare LA, Culbertson HS, Connors JJ 3rd. Intracranial angioplasty and stenting: long-term results from a single center. AJNR Am J Neuroradiol. 2006;27:1882–1892.
27. Zaidat OO, Fitzsimmons BF, Woodward BK, Wang Z, Killer-Oberpfalzer M, Wakhloo A, Gupta R, Kirshner H, Megerian JT, Lesko J, Pitzer P, Ramos J, Castonguay AC, Barnwell S, Smith WS, Gress DR; VISSIT Trial Investigators. Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: the VISSIT randomized clinical trial. JAMA. 2015;313:1240–1248.
28. Alexander MJ, Zauner A, Chaloupka JC, Baxter B, Callison RC, Gupta R, Song SS, Yu W, WEAVE trial sites and investigators. WEAVE trial: final results in 152 on-label patients. Stroke 2019 Apr;50(4): 889-894
29. Peng Gao, et al. China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS): A Prospective, Multicenter, Randomized Controlled Trial After SAMMPRIS. Stroke. 49:A64.
30. Kernan WN, et al. On behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:2160–2236
31. Kim H, Al-Shahi Salman R, McCulloch CE, Stapf C, Young WL; MARS Coinvestigators. Untreated brain arteriovenous malformation: Patient level meta-analysis of hemorrhage predictors. Neurology. 2014;83:590–597.
32. Wu EM, El Ahmadieh TY, McDougall CM, Aoun SG, Mehta N, Neeley OJ, Plitt A, Ban VS, Sillero R, White JA, Batjer HH, Welch BG. Embolization of brain arteriovenous malformation with intent to cure: a systematic review.J Neurosurg 2019 Feb:1-12 [Epub ahead of print]
33. Mohr JP, Parides MK, Stapf C, Moquete E, Moy CS, Overbey JR, Al- Shahi Salman R, Vicaut E, Young WL, Houdart E, Cordonnier C, Stefani MA, Hartmann A, von Kummer R, Biondi A, Berkefeld J, Klijn CJ, Harkness K, Libman R, Barreau X, Moskowitz AJ; International ARUBA Investigators. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomized trial. Lancet. 2014;383:614–621.
34. Tsang ACO, Hwang AC, Chiu RHY, Chan DYC, Tsang FCP, Ho WS, Lee R, Leung GKK, Lui WM. Combined aspiration thrombectomy and continuous intrasinus thrombolysis for cerebral venous sinus thrombosis: technical note and case series. Neuroradiology 2018 Oct;60(10):1093-1096
35. Siddiqui FM, Banerjee C, Zuurbier SM, Hao Q, Ahn C, Pride GL, Wasay M, Majoie CB, Liebeskind D, Johnson M, Stam J. Mechanical thrombectomy versus intrasinus thrombolysis for cerebral venous sinus thrombosis: a non-randomized comparison. Interv Neuroradiol. 2014;20:336–344.
36. Satti SR, Leishangthem L, Chaudry MI. Meta-analysis of CSF diversion procedures and dural venous sinus stenting in the setting of medically refractory idiopathic intracranial hypertension. AJNR Am J Neuroradiol. 2015;36:1899–1904.
37. Yang IH, Pereira VM, Lenck S, Nicholson P, Orru E, Klostranec JM, Krings T, Tsang ACO. Endovascular treatment of debilitating tinnitus secondary to cerebral venous sinus abnormalities: a literature review and technical illustration. J Neurointerv Surg 2019 Aug;11(8):841-846

Dermatology Quiz

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Specialist in Dermatology & Venereology

Dr Lai-yin CHONG

Fig. 1: Multiple papules on coronal sulcus of the glans penis

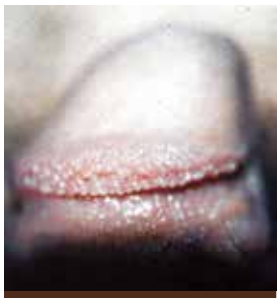

Fig. 2: Close-up view of the lesions

This 20 year-old male had a history of unprotected sex with a commercial sex worker (CSW) one month earlier. He was quite worried that he might have acquired sexually transmitted infections (STIs) following the encounter. On self-examination, while taking a bath, he noticed multiple asymptomatic papules on his glans penis (Fig. 1 and 2). He consulted a doctor and was told that he had STI. He was then treated with cryotherapy but with limited response.

Questions

1. What is your diagnosis and and what are the differential diagnoses?
2. What is your treatment for these lesions?
3. What laboratory tests would you order in this patient?

(See P.41 for answers)

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Endoscopic Spine Surgery - Current Development in Hong Kong

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INTRODUCTION

The two most common indications for surgery on the spine are to decompress the neural elements (spinal cord or nerve root) by (1) removing herniated intervertebral disc or (2) relieve of spinal stenosis, with the removal of part of the lamina, ligamentum flavum, and facet joints. Lumbar discectomy was first described by Oppenheim and Krause in 1909[1]. Since then, complete laminectomy and discectomy was the standard treatment. Although spinal elements were decompressed, the collateral damages to the spinal structures, including the facet joints, ligaments, and paraspinal muscles were high. Creating much bleeding, inflammation and extensive scar tissue around the dura and spinal nerves would significantly affect the short and long term outcome of the patient. Since the 1990s, one branch of the spine surgeons started to use a microscope with or without a tubular retractor to perform the minimally invasive spine surgery (MISS). Using these refined surgical techniques, SPORT trial showed patients suffering from lumbar disc herniation fulfilling appropriate indications achieved greater improvement with surgery compared to without surgery.[2] Collateral damages were reduced, and yet, partial laminotomy and medial facetectomy were still needed. These damages generated much epidural scar and destabilised the spine in some cases, leading to failed back surgery syndrome. General anaesthesia was also needed with MISS.

In a parallel world, in the 1960s to 1980s, another branch of the spine surgeons started to use the percutaneous technique in removing the herniated disc. Schreiber et al was the first to have the idea to perform this percutaneous nucleotomy under visual control using an endoscope.[3] Since then, many surgeons incorporated the endoscopic surgical technique into spine surgery, leading to the birth of Endoscopic Spine Surgery (ESS). In the 1990s, there were a few important improvements in technology: (1) use of continuous irrigation to reduce intra- and post-operative bleeding, to reduce infection rate and to improve vision of operation field, (2) using rongeurs and high-speed drills through the endoscope to remove the bony element and enlarge the operation window, (3) using underwater, bipolar radiofrequency probe for hemostasis, (4) using both the transforaminal and interlaminar approach in lumbar discectomy. The fast development of high-quality rod-lens based endoscope, high definition and 4K electronic camera, endoscopic low-temperature high frequency bipolar radiofrequency technology for hemostasis and tissue ablation, and use of laser for ablation via endoscope, make it possible to put all the surgical instruments in an endoscope of < 1cm in diameter and perform the traditional spinal decompressive surgery via a single port endoscope. The first sets of commercially available single port spinal endoscope were made in the 1990s. The endoscope was introduced over a guidewire and dilator, make it possible to perform surgery under local anaesthesia. It was not until the late 2000s that randomised trials comparing endoscopic lumbar discectomy and open or mini-open lumbar discectomy provide evidence that the endoscopic approach has a non-inferior outcome and less damage to spinal structures.[4] The initial learning curves were steep, facing significant complications in the initial 10 cases, but subsequent cases demonstrated improved outcomes.[5] The 1st of July 2017 was a major milestone towards the acceptance of endoscopic spine surgery (ESS) techniques and its benefits to both the surgeon and their patients. On that date, the American Medical Association approved the first billable CPT code to cover endoscopic decompression of the spinal cord, nerve root(s), including laminotomy, partial facetectomy, foraminotomy, discectomy and/or excision of the herniated intervertebral disc. Endoscopic discectomy becomes a recognised option of treatment of lumbar herniated disc. The complication rate for experienced surgeons is very low.[6] Alongside the development of endoscopic discectomy, a variant technique of single port or bi-portal endoscopic foraminotomy and laminectomy techniques has been developed as a replacement of traditional or microscopic surgery for spinal stenosis. With the reduction in the iatrogenic collateral damages, endoscopic decompression of spinal stenosis can be performed under local anaesthesia as a day case.[7]

CLINICAL APPLICATIONS IN HONG KONG

In Hong Kong, the first set of the single port endoscope for spinal surgery was introduced in the 2000s in the public sector and 2011 in the private sector. The first set was known as the YESS endoscope based on the design by Dr Anthony Young and associates in 1997, for both the interlaminar and transforaminal approach in lumbar discectomy, The interlaminar approach was familiar to surgeons performing traditional or MISS discectomy. However, the interlaminar approach required retraction of the spinal nerve root within the spinal canal during the discectomy and was associated with a higher chance of dural tear pseudocyst formation. The initial transforaminal endoscopic discectomy (TED) was based on the "inside-out" technique described by Dr Anthony

Young as follows: "first safely accessing the disc, then selectively removing disc tissue from the base of the herniation and pulling the extruded nucleus back within the disc and out via the cannula. Then the cannula could be manipulated to access the epidural space, lateral facets, and foramen and to inspect the traversing and exiting nerve roots". However, this technique was usually applied to the bulging disc or to the herniated disc fragment close to the annulus. It was not easy to treat sequestrated and migrated disc using this method. Hence, the application was narrow, and the use was not popular in Hong Kong.

In 2015, a different set of the spinal endoscope, known as Transforaminal Endoscopic Surgical System for TED was introduced to Hong Kong. The set of the endoscope was based on the design of Dr Thomas Hoogland in 1994, including the use of guidewire, dilators, operation cannulas, trephines, and bone reamers. The principle of the technique was an enlargement of the intervertebral foramen then direct fragmentectomy, i.e. endoscope was placed directly to the herniated, migrated or sequestrated disc fragment at the intervertebral foramen or spinal canal without entering the intervertebral disc itself. Upon the introduction of the high definition composite electronic camera and manual and powered bone drill for enlarging the intervertebral foramen, the application of the endoscope on the removal of the herniated disc then became much wider. The diameter of the endoscope is smaller, yet the working channel was larger. This allows almost all the surgery to be performed under awake conditions under monitoring by an anaesthetist. The constant feedback by the patient on the lower limb function was reassuring to the surgeon and patient that the neural elements were well protected during the surgery. Large prolapsed disc fragments could be removed under awake conditions. (Fig. 1 & 2) The development of TED escalated rapidly with a broadening of indications, an increase in the number of patients, an improvement in success rate and a reduction in complication rate. The proportion of patients with a herniated disc that can be treated by TED depends on the experience of the individual surgeon.

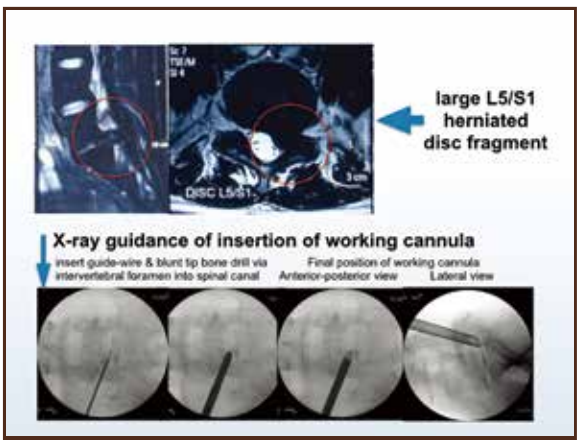

Fig. 1. Left L5/S1 Transforaminal endoscopic lumbar discectomy (TED).(Images from personal collection)

Fig. 2. left L5/S1 Transforaminal high definition endoscopic view. (Photos from personal collection)

Building on the confidence with experience, the spine surgeon now addresses the elderly patient with combined herniated disc and bony foraminal stenosis and even the elderly patient with low grade spondylolisthesis or scoliosis via a combined TED and foraminoplasty under local anesthesia, thus reducing anesthetic-related complication on the elderly. The technique and outcome were described by Madhavan K, et al in 2016.[8]

The other major indication for spinal surgery is the decompression of spinal stenosis in the older population. Decompressive laminectomy is the standard of care; however, trauma to the spinal structure and associate large epidural scar often causes the continuation of pain and neurological symptoms after surgery. The extensive removal of the lamina, the facet joint, and paraspinal muscle detachment causes iatrogenic instability, thus increasing the risk of subsequent neurological deterioration. Since 2016, ever-improving sets of the dedicated spinal endoscope instruments for interlaminar spinal decompression have been introduced. This endoscope provides a wider working channel for high-speed diamond bone drill and flexible tip Kerrison bone punch to make the decompression procedure more efficient. Under continuous fluid irrigation, the surgeon can see the dural sac and spinal nerve root directly to confirm adequate decompression. We have used this on the lumbar foraminotomy and in posterior cervical foraminotomy (Fig. 3 & 4).

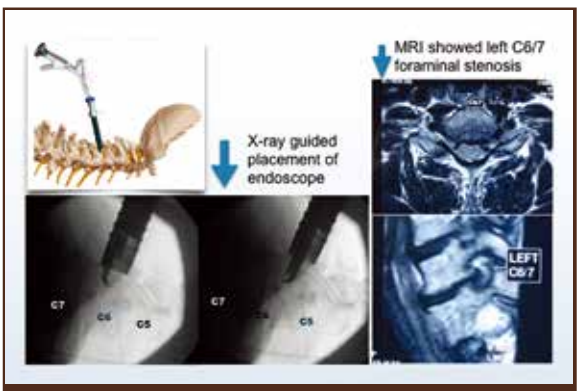

Fig. 3. left C6/7 Posterior Cervical Endoscopic Foraminotomy. (The drawing on endoscope were provided by representative of Joimax GmBh for education purpose.)

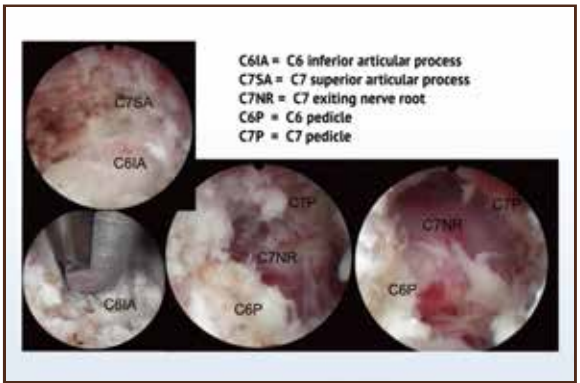

Fig. 4. left C6/7 Foraminotomy, high definition endoscopic view. (Photos from personal collection)

Endoscopic spinal surgery usually is performed under intra-operative C-arm X-ray guidance which helps to define the best trajectory in placing the endoscope. In 2019, Hong Kong is the first place in the world to combine the use of an O-arm2™ intraoperative 3D computerised scanning system, electromagnetic navigation system and spinal endoscope system in performing ESS. The combination provides more accurate three-dimension guidance in the placement of endoscope, without any radiation exposure to staff working in the operation room during the surgery. Moreover, intraoperative O-arm2™ 3D scanning at the end of the surgery can reassure there is good decompression of the bony spinal canal and foramen. O-arm navigation has been used successfully for TED (Fig. 5) and for interlaminar endoscopic lumbar foraminotomy (Fig. 6 to 9)

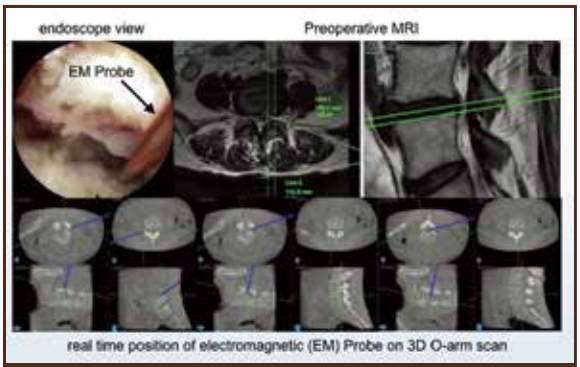

Fig. 5. O-arm Navigated left L4/5 transforaminal endoscopic lumbar discectomy and foraminotomy. (Photo and images from personal collection)

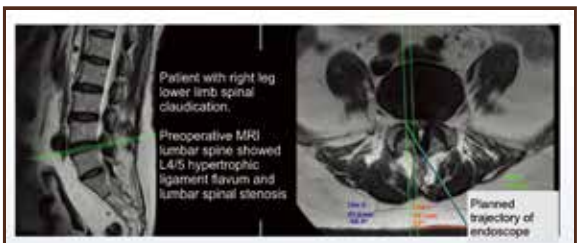

Fig. 6. O-arm Navigated right L4/5 interlaminar endoscopic lumbar foraminotomy (IELF). (Images from personal collection)

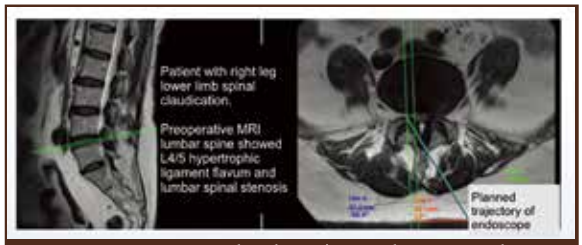

Fig. 6. O-arm Navigated right L4/5 interlaminar endoscopic lumbar foraminotomy (IELF). (Images from personal collection)

Fig 7. O-arm Navigated right L4/5 IELF. (Photos from personal collection)

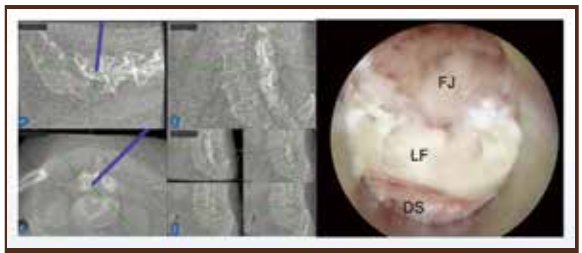

Fig. 8. O-arm Navigated right L4/5 IELF. Navigation showing the real-time position of the endoscope (left) and corresponding endoscopic view on the right of (1) drilled facet joint (FJ), (2) hypertrophic ligamentum flavum (LF) & (3) dura sac (DS) in the midline. (Photo and images from personal collection)

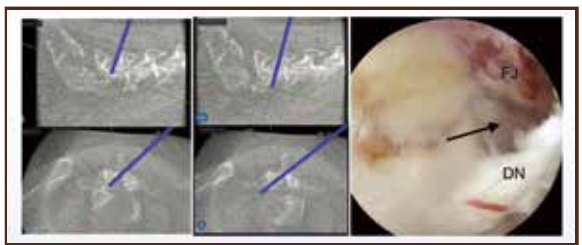

Fig. 9. O-arm Navigated right L4/5 IELF. Navigation showing endoscope has reached contralateral foramen through the foraminotomy (left) & endoscopic view (right) of drilled Facet Joint (FJ), Descending Nerve root (DN) and no ligamentum flavum between the nerve root and the drilled facet joint (black arrow). (Photo and images from personal collection)

To further the development of spinal endoscopy, we have extended the indication to posterior foraminotomy in the cervical spine, thoracic spine laminotomy, thoracic intervertebral discectomy (a technique described by Ruetten S et al 2018)[9], endoscopic assessed oblique lateral lumbar interbody fusion (a technique described by Kim JS et al, 2017).[10] The range of applications of ESS in Hong Kong can be described as "avant-garde" in comparison to other countries.

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CLINICAL RESULTS

We lack territory-wide statistics on endoscopic spine surgery. Unpublished personal experience of over 300 endoscopic spinal procedures are as follows: most of the procedures were on herniated lumbar intervertebral disc via the transforaminal endoscopic discectomy (TED). Of the 214 patients who underwent TED +/- transforaminal foraminoplasty, 93% have a good or excellent outcome as measured by patient perception. The good or excellent outcome patients had resolution of sciatica, no need for medications and had either mild or no residual back pain or leg discomfort. 4.7% developed recurrence (within a mean follow-up of 42 months), 2.8% required another lumbar discectomy (endoscopic or microscopic) and 1.4% required a lumbar spinal fusion; no patient developed paraplegia or monoplegia after surgery. 45% and 85% of our patients could be discharged one or two days after surgery, respectively. Our outcome is not inferior to the reported historical outcome. According to the Korean territory-wide statistics, the cumulative reoperation rate was 7.4% at 1 year and 13.4% at five years. The reoperation rates were 18.6%, 14.7%, 13.8%, 12.4% and 11.8% after laminectomy, nucleolysis, open discectomy, endoscopic discectomy, and fusion, respectively. (Kim CH et al, 2013) .[11]

SUMMARY

During the last decade, there has been a rapid development of endoscopic spinal surgery (ESS) in the world, including Hong Kong. It is now recognised as one of the standard procedures in spinal surgery. Herniated discs or spinal stenosis can now be treated using ESS instead of open or MISS. Cutting-edge ESS instruments are available in HK. We look forward to another decade of rapid development of ESS.

References

1. Oppenheim H and Krause F, "Ueber Einklemmung bzw. Strangulation der Cauda equina," Deutsche Medizinische Wochen- schrift, vol. 35, no. 16, pp. 697–700, 1909.
2. Weinstein JN et al. Surgical versus Non-Operative Treatment for Lumbar Disc Herniation: Four-Year Results for the Spine Patient Outcomes Research Trial (SPORT). Spine (Phila Pa 1976). 2008 Dec 1; 33(25): 2789–2800.
3. Schreiber A, Suezawa Y, and Leu H, "Does percutaneous nucleotomy with discoscopy replace conventional discectomy? Eight years of experience and results in treatment of herniated lumbar disc," Clinical Orthopaedics and Related Research, no. 238, pp. 35–42, 1989.
4. Ruetten S et al. Full-endoscopic interlaminar and transforaminal lumbar discectomy versus conventional microsurgical technique: A prospective, randomized, controlled study. SPINE Volume 33, Number 9 (2008)
5. Wang, B., G. Lu, A. A. Patel, P. Ren and I. Cheng (2011). "An evaluation of the learning curve for a complex surgical technique: the full endoscopic interlaminar approach for lumbar disc herniations." Spine Journal 11(2): 122-130.
6. Kim et. Al. Targeted percutaneous transforaminal endoscopic discectomy in 295 patients: comparison with results of microscopic discectomy. Surgical Neurology 68: 623-631 , 2006.
7. Kamson S, et al, "Full- endoscopic assisted lumbar decompressive surgery performed in an outpatient, ambulatory facility: Report of 5 years of complications and risk factors," Pain Physician, vol. 20, no. 2, pp. E221–E231, 2017.
8. Madhavan K, et al. Early experience with endoscopic foraminotomy in patients with moderate degenerative deformity. Neurosurg Focus Volume 40 • February 2016
9. Ruetten S et al, Full-endoscopic uniportal decompression in disc herniations and stenosis of the thoracic spine using the interlaminar, extraforaminal, or transthoracic retropleural approach, Journal of Neurosurgery: Spine, vol. 29, no. 2, pp. 157–168, 2018.
10. Kim JS et al. Endoscope-assisted oblique lumbar interbody fusion for the treatment of cauda equina syndrome: a technical note. Eur Spine J. 2017 Feb;26(2):397-403
11. Kim CH et al. Reoperation rate after surgery for lumbar herniated intervertebral disc disease: nationwide cohort study. Spine (Phila Pa 1976). 2013 Apr 1;38(7):581-90.

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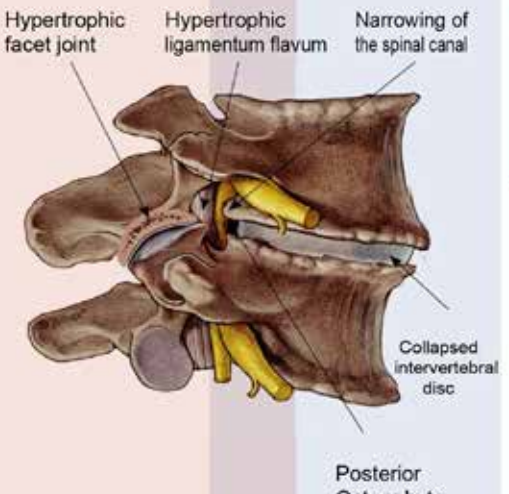
Problems with degenerative diseases



Advantages of endoscopic spine surgery

- Minimally invasive intervention, possible under local anesthetic
- Tissue-conserving surgical access
- Minimal destabilization and traumatization
- Visual endoscopic control of treatment
- Small incision, therefore hardly any scar tissue
- Short regeneration time and rapid return to everyday life

Endoscopic vs. conventional open discectomy*

Parameter	PETD group (TESSYS®)	Open group	P value
Operation time (min)	94.5± 23.9	148.1± 33.2	<0.001
Estimated blood loss (ml)	18.1± 9.7	308.6 ± 240.7	<0.001
Drainage (ml)	42.0± 78.4	185.0± 98.3	<0.001
Blood transfusion	0	3	<0.001
Postoperative hospitalization stay	3.5± 1.6	7.7± 4.0	<0.001

*Zquan Li et. al.; „Percutaneous Endoscopic Transforaminal Discectomy versus Conventional Open Lumbar Discectomy for Upper Lumbar Disc Herniation: A Comparative Cohort Study"; In: Hindawi, BioMed Research International, Volume 2020, Article ID 1952070, 7 pages. https://doi.org/10.1155/2020/1952070

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Artificial Intelligence: From a Neurosurgeon's Perspective

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INTRODUCTION

Artificial intelligence (AI) has been used vastly in our daily lives; examples include search engines and chatbots in the internet, advertisement in social media, spam filters in emails, voice recognition in smartphones, and the technology behind automated driving vehicles. Neurosurgery has been a sophisticated specialty in medicine characterised by high complexity in disease symptomatology, and imaging tests, and by treatment regimens and operations requiring high surgical skills and technology. Consequently, the use of AI and robots has always been an interest of neurosurgeons. In this article, I would like to review some of the key issues in AI in Neurosurgery, from a neurosurgeon's perspective.

ARTIFICIAL INTELLIGENCE (AI) AND ROBOTS

Artificial intelligence is a branch of computer science dealing with the simulation of intelligent behaviour in computers. There are various developments in AI. In conventional programming, the output is generated upon processing input data. In contrast, Machine learning (ML) is a learned programme from which the data from previous inputs and outputs are studied directly. The computer algorithms then learn the patterns from experience without being explicitly programmed. Subsequently, new outputs will be generated by new inputs. Different types of algorithms used in ML include supervised learning, unsupervised learning algorithms and reinforcement learning.

In reinforcement learning, it focuses on the determination of the ideal behaviour within a specific context based on simple reward feedback on their actions; it also explores an uncharted data territory like Google's DeepMind supercomputer that beats human intelligence in the game GO. Reinforcement learning is not widely applicable in Neurosurgery and thus will not be described here.

In supervised learning, supervised algorithms are usually used to train the computer using a set of inputs (such as Magnetic Resonant Imaging brain scans) as well as using a corresponding set of known outputs (such as the correct diagnosis of each scan). With each additional training set, the machine refines a mapping function which relates the input to the output with increasing precision. When the function sufficiently describes the relationship between the inputs and outputs, the learning stops and the machine can apply its training to a new input dataset (such as to diagnose a previously unseen MRI scan).

Artificial neural network (ANN) is one of the algorithms used in supervised learning. It makes use of a computational model based on the functioning of biological neural networks. It can be used for non-linear statistical data modelling with which the complex relationships between inputs and outputs (observed data) are modeled, and patterns are revealed. The ANN methodology involves three basic steps, namely data collection, data division and reduction to practice. The advantage of neural networks over conventional programming lies in their ability to solve problems that do not have an algorithmic solution, or whose available solution is too complex to be readily determined. ANNs are well suited to address solvable problems or dilemmas such as prediction, clinical diagnosis determination, pattern recognition and image analysis and interpretation. Examples of other supervised learning include support vector machine (SVM), decision tree, K-nearest neighbours (KNN) and Naïve Bayes algorithms.

For unsupervised learning, there is no training phase and the algorithms are left to form its own associations based on inherent groupings in the data. For instance, an unsupervised algorithm might analyse raw patient demographics found in hospital charts and deduce that female smokers are more likely to develop cerebral aneurysms than the general population. Fuzzy C-means is an example of unsupervised learning.

To facilitate AI, big data have to be available to allow accurate analysis of the data and fast computers have to process great calculating power of the tremendous amount of data.

APPLICATIONS IN NEUROSURGERY

Diagnosis

The major use of AI in Neurosurgery currently is in the diagnosis of disease conditions in different imaging modalities. AI is at least at good as expert neuroradiologists or neurosurgeons in the diagnosis of common brain tumours after machine learning of only 33 to 126 known diagnostic sets[9]. AI has been showed to be useful in the imaging diagnosis and grading of tumour in gliomas and paediatric posterior fossa tumours[1, 21]. In ischaemic stroke, AI application has been useful for analysis of Computed Tomography

(CT). Another field that AI might be useful is the interpretation of electroencephalography (EEG) to predict epilepsy[5].

Decision-making in Treatment

Machine learning (ML) might be useful in Neurotraumatology in the prediction of intracranial pressure (ICP) based on ICP and other data to guide treatment[18]. There have also been studies on ML algorithms for non-operative treatment for spinal epidural abscess and for postoperative opioid prescription after lumbar disc operations[12, 17].

Preoperative planning

The application of AI in imaging would allow surgeons to locate the target lesion accurately and to appreciate its relation with the delicate surrounding neurovascular tissues. Segmentation technology allows surgeons to study the relationship between the target lesions and surrounding brain tissues in details. This technology is currently applicable in commercially available Neuronavigation programmes.

In addition, AI is useful in simulation and training of surgical operations. Neurosurgeons, both practising specialists and trainees, would benefit from the computer simulators, virtual reality (VR) and augmented reality (AR).

Robotic Surgery

In neurosurgical operations, we often have to work in delicate neural tissues in narrow and confined corridors. Robots offer the advantages of the provision of fine instruments with high localisation accuracy and great stability eliminating muscle fatigue and physiologic tremors during long operations. Robots are also useful to provide tedious, repetitive works. Robots would enhance the surgical performance of the surgeons.

Different involvement in AI in robotic operations has been described. Robots have been used in surgical microscopes (MKM by Zeiss and SurgiScope by ISIS Robotics) to direct the neurosurgeons to the surgical field of the target lesions in the 1990s and 2000s.

Robot-assisted surgery involves the use of robots for accurate localisation of targets in stereotactic biopsies. In Functional Neurosurgery for diseases like Parkinson's Disease, robots can be used in electrode placement in Deep Brain Stimulation (DBS). In stereotactic electroencephalography (SEEG) for epilepsy, robots can assist in the placement of multiple microelectrodes into the epileptogenic foci in an accurate and fast manner. In addition, robots can also be used in target ablation in radiosurgery. Since the introduction of the PUMA 200 for brain biopsy in 1985, there have been numerous examples of robotic systems in Neurosurgery including NeuroMate, Pathfinder, Neuroarm, Spine assist, Renaissance, the Steady Hand system, Neurolocate, iArms, EXPERT system, iSYSI Robot, Spinal robotics, Augmented Reality systems, Neurosurgical lasers, da Vinci robot, SOCRATES and ROSA. In spine surgery, robots are also used in the accurate placement of pedicle screws. Other than surgery, robots might be helpful in brain mapping in transcranial magnetic stimulation (TMS)[8].

However, there are challenges to the use of robots in surgery. Surgeons often rely on tactile sensation to guide the operation, and it is challenging to give the operator tactile feedback in robotic surgery. The sense of touch gives us information on the material properties of an object, including stiffness (elasticity), texture and weight; as well as shape properties such as size, orientation and curvature. When human explores an object, we do so by identification of texture through lateral motion, hardness by applying pressure, temperature through static contact, weight by unsupported holding, global shape and volume through enclosure by fingers, and exact shape by following the object contours.

In robotic engineering, haptics refers to a field of study that seeks to produce realistic interaction between a human and a remote or virtual environment. To produce realistic tactile and kinesthetic feedback between a human and environment felt only indirectly, engineers use haptic interfaces that relay tactile properties and kinesthetic (force) feedback from a virtual or robotic proxy back to the human who operates it[13].

In addition, neurosurgeons operate within severe spatial constraints, and the consequences of any tissue or vascular injury would be catastrophic. It is noted that although the non-diagnostic rates and mortality rates for robotic-assisted cranial stereotactic procedures were comparable to manual procedures, the rate of intracranial haemorrhage in robotic procedures was 4% more than the latter group[10].

Another potential development for robotic surgery in the future would be telesurgery to allow surgeons to operate in remote and distant locations. There has been a study in remote operation of a pituitary tumour in Nashville[20]. The surgeon controlled a robot connected with a dedicated network in 800 kilometres away from the hospital. The dedicated network ensured fast communication between the surgeon and the robot with latency below 200 milliseconds (ms). It was found that with a video latency of less than 100 ms, all surgeons gave a good surgeon safety perception score.

Treatment Modulation by AI

In Deep Brain Stimulation (DBS), intelligently-delivered close-loop DBS devices are being developed and coupled with algorithms within the device to detect patterns highly suggestive of impending seizures followed by automatically deliver electrical stimulation to abort the seizure. Such close-loop DBS devices might also be useful in Parkinson's Disease to sense the subcortical oscillations and to deliver ramped electrical stimulation to the subthalamic nucleus to achieve substantial improvement in patients' clinical symptoms[3].

OUTCOME PREDICTION

AI might help in outcome prediction in the various neurosurgical conditions. There have been studies

looking at the predicted outcome of epilepsy surgery, of Parkinson's Disease after DBS, of gliomas and metastases after surgery, of aneurysm clipping, of radiosurgery, of endovascular treatment for arteriovenous malformation (AVM) and and of spine surgery for degenerative spine disorders. In addition, AI is able to predict the postoperative stay according to the operation reports.

LIMITATIONS

The mechanisms underlying ML models can be difficult to interpret and scrutinise. However, the introduction of a new technique into clinical care without universal understanding is not a new concept. With time, clinicians are getting more familiar and more comfortable to deploy them in clinical practice.

As discussed below in the section of ethics, clinicians should retain the ultimate responsibility to the patients in the diagnosis and treatment. There have arguments about the regulation on performance standards of the implemented ML models. Furthermore, it can be argued whether the manufacturer of the ML algorithms should freeze the learning process after production and deliver static models alone, or institutions should be allowed to augment performance by means of setting specific training data (referred as "training on the job").

Lastly, the performance of ML is highly dependent on the quality of input data. Insufficient data and biased data would affect the quality and thus, the performance of ML.

ETHICS

As Artificial Intelligence (AI) and robots are involved more and more in the diagnosis and treatment, they introduce themselves as the third party in the physician-patient relationship. However, it would still be the neurosurgeons who remain responsible for the patients' well being, and we cannot blindly follow the predictions or steps made by AI. AI-enabled devices have to incorporate robust and redundant safety features in their design to mitigate potential complications. In the near future, it is expected that the public would still not accept treatment relying on AI or robot alone for safety issues and as part of human nature.

In addition, for the intelligently delivered DBS devices to work, interrogation and troubleshooting of the system should be easily accessible at all times, and the device should have wireless capabilities to allow quick reprogramming or even reliance on cloud-based computing to update the algorithm. The possibility of privacy breaching and hacking of devices should not be overlooked.

As a final rule, even though machine learning makes it possible to allow AI to learn from its own, the rewriting of the operating programmes by AI itself should not be allowed.

CONCLUSION

Technological advancement in the analysis of big data and artificial intelligence (AI), as well as robots in surgeryl, has made it possible to use AI in the disease diagnosis. Robotic-assisted surgery is currently applicable to stereotactic biopsies and Functional Neurosurgery to supplement and assist the neurosurgeons in improving accuracy and in decreasing risks for surgical treatment. However, there are still obstacles to the future development of AI and robots such as the lack of tactile sensation in surgical robots and ethical issues, making complete automated surgery unlikely in the near future.

References

1. Arle J et al. Prediction of Posterior Fossa Tumor Type in Children by Means of Magnetic Resonant Image Properties, Spectroscopy and Neural Networks. J Neurosurg 1997; 86(5): p.755-761.
2. Azimi P et al. Artificial Neural Network in Neurosurgery. J Neurol Neurosurg Psychiatry 2015 (86): p251-256.
3. Beudel M. Adaptive Brain Stimulation for Parkinson's Disease in Closed Loop. Neuroscience 2016.
4. Bhattacharyya D. The Effect of Machine Learning and Artificial Intelligence on the Use of Robots in Neurosurgery. ACNR May-July 2019; 18(4): p26-28.
5. Dunn-Henriksen J et al. Channel Selection for Automatic Seizure Detection. Clin Neurophysiol 2012. doi:10.1016/j.clinph.2011.06.001.
6. Celtikci E et al. A Systemic Review on Machine Learning in Neurosurgery: The Future of Decision-making in Patient Care. Turkish Neurosurgery 2018; 28(2): p167-173.
7. Chan S et al. Virtual Reality Simulation in Neurosurgery: Technologies and Evolution. Neurosurgery 2013 (72): A154-164.
8. Finke M et al. Brain Mapping Using Robotized Transcranial Magnetic Stimulation. Annual International Conference of IEEE Engineering in Medicine and Biology Society. 2008: p3929-32.
9. Fomenko A et al. Artificial Intelligence in Neurosurgery. UTMJ 2019; 96(1): p19-21.
10. Formenko A et al. Robotic Stereotaxy in Cranial Neurosurgery: A Qualitative Systemic Review. Neurosurgry 2018 (83): p642-630.
11. Ganapathy K et al. Neurology India 2018; 66: p934-939.
12. Karhade A et al. Development of Machine Learning Algorithms for Prediction of Prolonged Opioid Prescription after Surgery for Lumbar Disc Herniation. The Spine Journal 2019 (19): p1764-1771.
13. L'Orsa R et al. Introduction to Haptics to Neurosurgeons. Neurosurgery Jan 2013 (72): A139-153.
14. Senders J et al. An Introduction and Overview of Machine Learning in Neurosurgical Care. Acta Neurochir 2018 (160): p29-38.
15. Senders J et al. Machine Learning and Neurosurgical Outcome Prediction: A Systemic Review. World Neurosurg 2018 (109): p476-486.
16. Senders J et al. Natural and Artificial Intelligence in Neurosurgery: A Systemic Review. Neurosurgery 2018; 83(2): p181-192.
17. Shah A et al. Development of Machine Learning Algorithm for Prediction of Failure of Non-operative Management in Spinal Epidural Abscess. The Spine Journal 2019 (19): p1657-1665.
18. Swiercz M et al. Intracrainal pressure processing with artificial neural networks: Prediction of ICP Trends. Acta Neurochir 142: p401-406.
19. Vassileva A et al. Neocortical Electrical Stimulation for Epilepsy: Closed Loop vs Open Loop. Epilepsy Res. 2018.
20. Wirz R et al. An Experimental Feasibility Study on Robotic Endonasal Telesurgery. Neurosurgery 2015; 76(4): p479-484.
21. Zhao ZX et al. A New Method to Classify Pathologic Grades of Astrocytomas Based on Magnetic Resonant Imaging Appearances. Neurol India 2010 (58): p685-690.

Transcending the Boundaries of Treating Brain Metastases

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INTRODUCTION

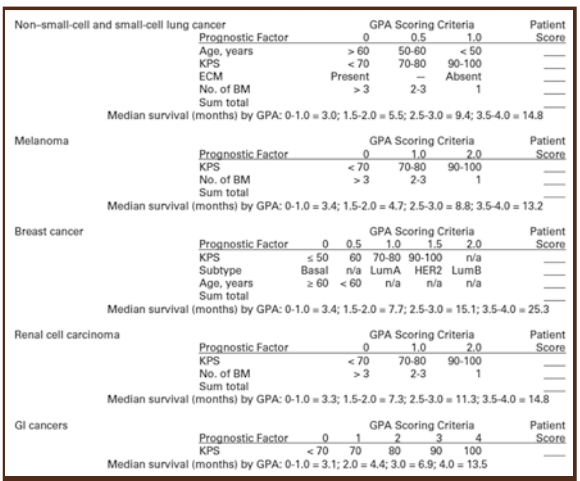
Brain metastases are the most common intracranial tumours in adults. With the improving efficacy of systemic therapy to extracranial disease, high accessibility to surveillance imaging and higher awareness of clinicians, the incidence of brain metastases is increasing. Even though the development of brain metastases brings patients to the final stage of different malignancies, numerous advancements in various established treatment options are blooming. Not only can the overall survival be prolonged, but also the quality of life of patients can be secured. To achieve such outcome, individualised treatment regimen with multidisciplinary collaboration is of utmost importance owing to the fact that this group of patients are indeed a heterogeneous population in terms of the primary tumour, number and size of brain metastases and different response to treatment options.

DIAGNOSIS OF BRAIN METASTASES

Intuitively, having a new headache, cognitive decline, neurological deficits and/or seizure with a background of malignancy prompts clinician to search for brain metastases. Among various malignancies, lung cancer, especially adenocarcinoma, and breast cancer both have a high propensity to metastasise to the brain. Whereas cancers from prostate, head and neck, oesophagus, ovary/uterus rarely develop brain metastasis. It should be noted that it is not uncommon for the primary tumour to initially manifest with symptomatic brain metastases without any prior histological diagnosis[1]. Moreover, brain metastases can also be detected incidentally in whole-body staging imaging or scans for other unrelated symptoms. Typical imaging modalities include whole-body PET scan (including the brain) and MRI brain scan. Serum tumour makers, albeit not diagnostic, also provides clues to differentiate brain metastases from a primary brain tumour. Furthermore, clinicians should not exclude the differential diagnosis of brain metastases/tumours in patients with intracerebral haemorrhage, especially not occurring at the typical sites of hypertensive haemorrhage, such as. basal ganglia, thalamus, cerebellum, etc. Brain metastases from renal cell carcinoma, thyroid carcinoma and hepatocellular carcinoma are at higher risk of bleeding.

PROGNOSTICATION TO GUIDE MANAGEMENT

Although published more than 20 years ago, prognostic factors derived from the Recursive Partitioning Analysis (RPA) of 1,200 brain metastases patients by Radiation Therapy Oncology Group (RTOG)[2] are still used nowadays to decide treatment regimen. Patients with age less than 65, Karnofsky Performance Status (KPS) of at least 70 and controlled primary tumour had the best overall survival when whole-brain radiation therapy (WBRT) was the only available treatment to brain metastases. With advances of systemic therapy, RTOG developed diagnosis-specific Graded Prognostic Assessment (dsGPA) for the patient with brain metastases in 2012.(Fig. 1)[3] Patients' survival will be estimated according to the primary tumour/subtype, age, presence of extracranial metastases and number of brain metastases.



Non-small-cell and small-cell lung cancer

Prognostic Factor	0	0.5	1.0	Patient Score
Age, years	> 60	50-60	< 50	___
KPS	< 70	70-80	90-100	___
ECM	Present	—	Absent	___
No. of BM	> 3	2-3	1	___
Sum total				___

Median survival (months) by GPA: 0-1.0 = 3.0; 1.5-2.0 = 5.5; 2.5-3.0 = 9.4; 3.5-4.0 = 14.8

Melanoma

Prognostic Factor	0	1.0	2.0	Patient Score
KPS	< 70	70-80	90-100	___
No. of BM	> 3	2-3	1	___
Sum total				___

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 4.7; 2.5-3.0 = 8.8; 3.5-4.0 = 13.2

Breast cancer

Prognostic Factor	0	0.5	1.0	1.5	2.0	Patient Score
KPS	≤ 50	60	70-80	90-100	n/a	___
Subtype	Basal	n/a	LumA	HER2	LumB	___
Age, years	≥ 60	< 60	n/a	n/a	n/a	___
Sum total						___

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 7.7; 2.5-3.0 = 15.1; 3.5-4.0 = 25.3

Renal cell carcinoma

Prognostic Factor	0	1.0	2.0	Patient Score
KPS	< 70	70-80	90-100	___
No. of BM	> 3	2-3	1	___
Sum total				___

Median survival (months) by GPA: 0-1.0 = 3.3; 1.5-2.0 = 7.3; 2.5-3.0 = 11.3; 3.5-4.0 = 14.8

GI cancers

Prognostic Factor	0	1	2	3	4	Patient Score
KPS	< 70	70	80	90	100	___

Median survival (months) by GPA: 0-1.0 = 3.1; 2.0 = 4.4; 3.0 = 6.9; 4.0 = 13.5

Fig. 1. Diagnosis-specific Graded Prognostic Assessment (dsGPA). The patient score, calculated from the summation of the individual score of each prognostic factors, is used to estimate the median survival. (Adapted from Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin Oncol. 2012;30(4):419-25.)

TREATMENT - SYMPTOMATIC

Symptoms from brain metastases can be caused by mass effect directly from the tumour or indirectly from the resulting cerebral oedema. Steroids, such

as dexamethasone at dosages of 4 - 16 mg/daily, are commonly used to reduce cerebral oedema before, during or after treatment of brain metastases. It should be used for 1-2 weeks with gradual tapering to avoid long-term side effects especially steroid-induced adrenal insufficiency[4]. Amelioration of symptoms can be observed within 1-2 days. Occasionally, patients may refuse or default subsequent treatments due to the immediate improvement of symptoms. As a result, patients should be primed that steroid is for symptomatic treatment of cerebral oedema only but not for treating the metastases. H2-blocker/proton pump inhibitor can be used concomitantly in patients at a high risk of developing peptic ulcers.

Anticonvulsants such as phenytoin, valproate, and levetiracetam should be given to the patients presented with seizure. Clinicians should be cautious about the side effects, such as. phenytoin-induced deranged liver function, and drug-drug interaction, such as phenytoin with warfarin, dexamethasone, before the prescription. However, the prophylactic use of anticonvulsants is not recommended[5].

TREATMENT - SURGERY

There are several advantages of surgical resection. Firstly, resection of large metastasis could lead to an immediate reduction of intracranial pressure and mass effect on brain. Hence, the immediate risk of mortality and morbidity due to neural injury could be reduced. A therapeutic time window is thus created for subsequent adjuvant treatments. Secondly, as mentioned previously, it helps histological diagnosis in patients who initially presented with symptomatic brain metastases. In addition, genomic variation is observed between the brain metastasis and the primary tumour.[6] Obtaining new tissue from brain metastases for diagnosis is therefore particularly helpful in choosing an effective targeted therapy. Thirdly, better progression-free survival, overall survival and functional status of gross total surgical resection of single brain metastasis with adjuvant whole-brain radiotherapy has been proven in a randomised controlled trial in patients with KPS > 70.[7]

Intraoperative monitoring of neurological function, navigation system and new haemostatic materials can also be adopted to effectively reduce surgical morbidities.

Other than neurological deficits and general neurosurgical complications such as infection and general anaesthesia complications, surgical resection also carries a risk of tumour seedling leading to meningeal metastases.

Surgery can be combined with other treatment options to achieve a better outcome, and will be discussed in subsequent sections.

TREATMENT – WHOLE BRAIN RADIOTHERAPY (WBRT)

Traditionally, brain metastases have been treated with whole-brain radiotherapy only. It is simple in planning and able to treat all intracranial diseases, including leptomeningeal metastases which is difficult to be excised or stereotactically targeted for radiosurgery. Nevertheless, the disabling side effect of cognitive decline from WBRT is infamous. The use of memantine[8] and hippocampal-avoidance radiotherapy planning[9] is a recent way to alleviate the severity. Other side effects of WBRT include fatigue, nausea, loss of appetite, and alopecia. It can be given as a sole treatment or as the standard adjuvant treatment after surgical resection to reduce recurrence[10].

TREATMENT – STEREOTACTIC RADIO-SURGERY/THERAPY (SRS/T)

Instead of subjecting the entire brain to radiation, high dose of ionising radiation can be precisely delivered to predefined locations with minimal harm to normal brain tissue by the use of linear accelerator or gamma knife in single or multiple sessions with ablative intent. As a result, significant cognitive decline from WBRT[11] and surgical complications, especially resection at eloquent areas, can be circumvented by SRS/T. This recently popular treatment modality alone has been included in various regional and international guidelines of brain metastases management[12, 13].

When it is performed on a single session, it is called stereotactic radiosurgery. It is applicable to brain metastases of size less than 3 cm after considering the higher risk of toxicity to the normal brain in treating larger metastases. With the advent of new computer software in planning (Fig. 2), the number of metastases simultaneously treated in a single session can be up to 15. In case of tumour size greater than 3 cm, multiple sessions, known as stereotactic radiotherapy or fractionated stereotactic radiosurgery, can be adopted to achieve the treatment effect. Patients can be treated without hospitalisation. The current trend is to deliver SRS/T in a non-invasive frameless manner while maintaining the accuracy and patients' comfort at the same time.

Other than the general side effects of radiotherapy aforementioned in WBRT section, one should be aware of radiation necrosis, which can be symptomatic and radiologically similar to tumour recurrence. Biopsy to differentiate necrosis from recurrence is infrequently required since there is no reliable imaging modality easily available for such purpose. Steroid or bevacizumab can be used to treat radiation necrosis.

Adjuvant SRS/T to resection cavity has been replacing adjuvant WBRT as the standard of care due to similar overall survival while retaining cognitive function.[14] The use of preoperative SRS/T is being explored because of the advantage of increased local control, decreased leptomeningeal disease, radiation necrosis; and improved systemic control due to sensitisation of immune system to kill tumour cells, known as abscopal effect. Unfortunately, preoperative radiation may change the pathology affecting the histological diagnosis and may also impair wound healing.[15]

Furthermore, due to minimal radiation effect to normal brain, tumour recurrence could be re-irradiated by SRS/T whereas repeating WBRT would definitely exceed the radiation tolerance of the normal brain.

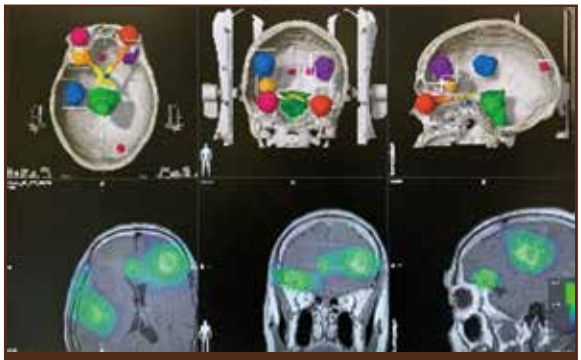


Fig. 2. New SRS/T treatment planning software to target multiple brain metastases . (Images from personal collection)

TREATMENT – SYSTEMIC CHEMOTHERAPY

This treatment option is usually of limited use because of the blood-brain barrier being able to block or pump out chemotherapy of large molecular size.

TREATMENT – TARGETED THERAPY

The use of targeted therapy in treating malignancies, especially lung and breast cancer, have been extensively studied for decades. Newer generations with better cerebrospinal fluid concentration have been developed and demonstrated better progression-free survival compared with older generations[16]. They target the mutations in the cell cycle/cell signalling pathways rendering cytotoxic properties of the drugs. Examples include EGFR, ALK inhibitors in lung cancer and HER2 Tyrosine kinase inhibitors in breast cancer.

TREATMENT – IMMUNOTHERAPY

There is rapidly growing evidence showing the promising result of using immune-checkpoint inhibitors, e.g. PD-1, PD-L1/2, CTLA-4 inhibitors. They stimulate the host immune system to kill the cancer cells. Use of dexamethasone would, therefore, impair the effect of such therapy.

CONCLUSIONS AND EXPERIENCE IN TUEN MUN HOSPITAL

Clinicians and scientists are putting joint efforts in developing new and advancing existing options in treating brain metastases. With such a large battery of treatments, balancing risks and benefits with patients, neurosurgeons, neuro-oncologists and medical physicists is the key to success in yielding favourable treatment outcomes. Fig. 3 is the treatment decision pathway in Tuen Mun Hospital.

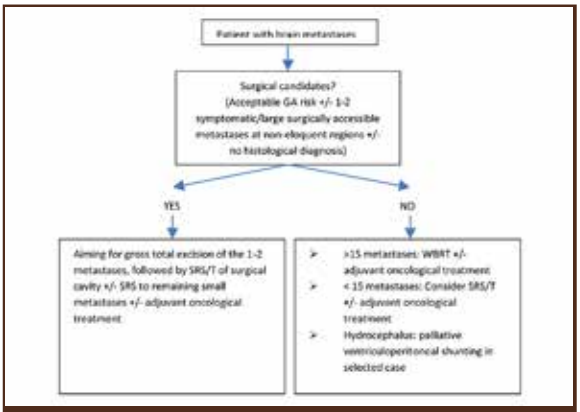


Fig. 3. Treatment decision pathway in Tuen Mun Hospital. (Developed by Dr Kwong-yui YAM and Dr Jason Man-kit HO)

In Tuen Mun Hospital, the neurosurgeons or the oncoclogists first identify whether the patient is a surgical candidate. If the patient carries an acceptable risk from general anaesthesia and is suffering from one to two exquisitely large metastases or large infratentorial metastasis with significant hydrocephalus or brainstem compression, in which raised intracranial pressure or significant neurological deficit is a concern, we would offer surgery to patients with surgically accessible and safe-to-resect metastases. Operations are usually done as soon as possible.

Postoperative adjuvant oncological treatment will be discussed preoperatively or within one week after operation in combined Neurosurgery and Oncology Clinic in order to formulate an individualised treatment plan and to arrange logistics for subsequent workup and treatment. We would offer SRT , due to size usually larger than 3 cm, to surgical cavity and SRS to remaining untreated small metastases. Efforts have to be made to shorten the time lag, usually within three weeks, between surgery and SRS in order to reduce early recurrence and manage the untreated metastases intracranially. Common causes of timg lag in our setting include waiting time for radiosurgery, obtaining PET scan with report and clinic waiting time for pre-adjuvant-therapy assessment.

If the patient is not a surgical candidate, we would try offering SRS/T as definitive treatment. We would try our best to avoid WBRT sparing patients from cognitive decline and upkeeping the quality of life for patients at their final stage of the disease.

References

1. Fureder LM, Widhalm G, Gatterbauer B, Dieckmann K, Hainfellner JA, Bartsch R, et al. Brain metastases as first manifestation of advanced cancer: exploratory analysis of 459 patients at a tertiary care center. Clin Exp Metastasis. 2018;35(8):727-38.
2. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys. 1997;37(4):745-51.
3. Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin Oncol. 2012;30(4):419-25.
4. Ryken TC, McDermott M, Robinson PD, Ammirati M, Andrews DW, Asher AL, et al. The role of steroids in the management of brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol. 2010;96(1):103-14.

5. Chen CC, Rennert RC, Olson JJ. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on the Role of Prophylactic Anticonvulsants in the Treatment of Adults with Metastatic Brain Tumors. Neurosurgery. 2019;84(3):E195-E7.
6. Brastianos PK, Carter SL, Santagata S, Cahill DP, Taylor-Weiner A, Jones RT, et al. Genomic Characterization of Brain Metastases Reveals Branched Evolution and Potential Therapeutic Targets. Cancer Discov. 2015;5(11):1164-77.
7. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med. 1990;322(8):494-500.
8. Brown PD, Pugh S, Laack NN, Wefel JS, Khuntia D, Meyers C, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro Oncol. 2013;15(10):1429-37.
9. Lin SY, Yang CC, Wu YM, Tseng CK, Wei KC, Chu YC, et al. Evaluating the impact of hippocampal sparing during whole brain radiotherapy on neurocognitive functions: A preliminary report of a prospective phase II study. Biomed J. 2015;38(5):439-49.
10. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA. 1998;280(17):1485-9.
11. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial. JAMA. 2016;316(4):401-9.
12. Brain tumours (primary) and brain metastases in adults. National Institute for Health and Care Excellence: Clinical Guidelines. London2018.
13. Chao ST, De Salles A, Hayashi M, Levivier M, Ma L, Martinez R, et al. Stereotactic Radiosurgery in the Management of Limited (1-4) Brain Metasteses: Systematic Review and International Stereotactic Radiosurgery Society Practice Guideline. Neurosurgery. 2018;83(3):345-53.
14. Kayama T, Sato S, Sakurada K, Mizusawa J, Nishikawa R, Narita Y, et al. Effects of Surgery With Salvage Stereotactic Radiosurgery Versus Surgery With Whole-Brain Radiation Therapy in Patients With One to Four Brain Metastases (JCOG0504): A Phase III, Noninferiority, Randomized Controlled Trial. J Clin Oncol. 2018:JCO2018786186.
15. Routman DM, Yan E, Vora S, Peterson J, Mahajan A, Chaichana KL, et al. Preoperative Stereotactic Radiosurgery for Brain Metastases. Front Neurol. 2018;9:959.
16. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2018;378(2):113-25.

Stereoelectroencephalography: A Methodical Process, Certainly Not a Fishing Expedition

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INTRODUCTION

The drug-resistant state occurs in up to one-third of epilepsy patients in spite of the development of new pharmaceutical agents[1]. It would be a great relief for these patients, if an "excisable" culprit in the brain is detected – the epileptogenic zone (EZ) – the minimal volume of the brain needs to be removed or disconnected to render the patient seizure-free[2,3,4].

The goal of pre-surgical workup in epilepsy surgery is primarily to identify the EZ. However, it is easier said than done even when provided with the most advanced imaging modalities and electroencephalography machinery, together with the concerted effort of an epilepsy surgery team. About 30-40% of patients undergoing epilepsy surgery workup in an epilepsy surgery centre require invasive electroencephalography (EEG), which refers to subdural strip/grid with or without depth electrodes, and stereoelectroencephalography (SEEG)[5].

SEEG is a method, not merely a technique. The terminology may give a false impression that it is a surgical procedure per se of implanting intracranial depth electrodes, or a standardised investigation akin to a scalp EEG. Rather, SEEG is an evaluation process for a highly selected group of patients with drug-resistant epilepsy. The SEEG method broadly consists of the following steps:

i) pre-implantation planning taking into account the available anatomo-electroclinical information,
ii) the intracranial depth electrode implantation procedure, and
iii) post-implantation recording with or without bedside electrical stimulation, and SEEG data analysis[6].

SEEG is not a novel concept. It was designed and developed in Paris in the 1960's. Technological advancements in medical imaging, intra-operative image guidance, and robot-assisted surgery, however, have enhanced its safety and clinical values, and also its implementation internationally[7].

EPILEPTOGENIC ZONE, SEEG ELECTRODES, AND THE NEED OF A STRATEGY

The definition of EZ has evolved to incorporate the epilepsy network concept, and the term epileptogenic zone network has been coined[6]. In epilepsy surgery, mapping the boundary of an EZ is surgically relevant only when the EZ is confined to one hemisphere, for the obvious reason that the maximal scale of resection or disconnection in epilepsy surgery is hemispherectomy (hemispherotomy). Thus, SEEG candidates are drug-resistant epilepsy patients with focal epileptic seizures, definite or possible. Focal epileptic seizures are conceptualised as originating within networks limited to one hemisphere. A network may be discretely localised or more widely distributed, and may originate in subcortical structures. Some patient may have more than one such network in the involved hemisphere[8].

In actual clinical practice, an EZ even in focal epileptic seizure patients can range from a very small region of the brain, such as 1 cm in diameter, to the whole involved hemisphere with an extensive network[9]. However, without the information from anatomo-electroclinical correlations derived from non-invasive epilepsy surgery workup, it would be impossible to map out an EZ, either small or extensive, even with SEEG. This difficulty is because of the vastness of the "innerverse" when the brain is examined at the cellular level[10]. There are 10-20 billion neurons in the human cerebral cortex, distributed over an area of 2,350 cm^2 (unfolded)[11,12].

Modern SEEG electrodes are made with platinum-iridium, generally 0.8 mm in diameter, with multiple contacts of 2 mm long and 1.5 mm apart. One electrode can have up to 18 contacts (Fig. 1). Despite the apparently minimal invasiveness of the electrode design, they do leave a MRI demonstrable tract in the brain. The number of electrodes used in one study, usually ranging between 6 and 15, with the mean of 11[7,13], must be judicious. Given that one contact on an electrode can sample a brain volume of just about 5 mm^3, it has been said that a SEEG study can only sample up to 1% of the brain[14], which explains why the main limitation of SEEG is the sampling bias. Thus, the need for a strategy when using SEEG is mandatory.

Fig. 1. A SEEG electrode with 15 contacts (diameter 0.8 mm), and a skull fixation bolt. (Photo from personal collection)

INDICATIONS FOR SEEG

There are no hard and fast rules about patient selection in SEEG. When a patient is being evaluated for drug-resistant epilepsy, the epilepsy surgery team's decision often depends on their available resources and expertise with the non-invasive modalities. Besides, SEEG and the other invasive monitoring method i.e. subdural grid/strip, are complementary to each other[7,15]. For example, in patients requiring language mapping, subdural grid/strip is the method of choice. One advantageous feature of SEEG electrodes is that they allow the application of radiofrequency thermo-coagulation for lesioning via the same electrode *in situ*[13].

In general, SEEG is indicated when anatomo-electroclinical information derived from non-invasive modalities is insufficiently concordant regarding the EZ, or when there is a main hypothesis with alternative hypotheses to eliminate[13].

SEEG is used both in patients with a lesion demonstrable by magnetic resonance imaging (MRI) (lesional), and in patients without a lesion (MRI-negative). In lesional cases, the roles of SEEG are as follows, i) to define the border of EZ in an extra-temporal lesion, ii) to identify the epileptogenic lesion among multiple lesions as in tuberous sclerosis, iii) to confirm the hypothesis when EZ is suspected to be not related to a lesion, and iv) to confirm unilateral involvement in mesial temporal lobe pathology with early contra-lateral involvement. In MRI-negative cases, SEEG can be used to define the EZ where non-invasive modalities, such as a scalp EEG with/without positron emission tomography, show focal seizures. This strategy applies both to temporal lobe and extra-temporal lobe epilepsies[13].

THE SEEG METHODOLOGY

When SEEG is deemed by an epilepsy surgery team to be indicated in a patient, the next phase of action is pre-implantation evaluation, preparation and planning. First, there is an overall assessment of the risk-benefit ratio of a SEEG, followed by a thorough discussion about it with the patient and guardians. After a consensus is reached among the managing team, the patient and the guardians, the technical workflow is as follows: i) A hypothesis (hypotheses) of the EZ based on the available anatomo-electroclinical data is (are) reviewed. ii) Dedicated SEEG MRI sequences and angiography are performed. iii) The cerebral targets to be studied with SEEG are defined with multidisciplinary input. iv) The SEEG electrode trajectories are then planned[13].

The surgical procedure of SEEG electrode implantation is performed under general anaesthesia. The pre-defined electrodes are inserted under stereotactic guidance, which can be a frame-based, frameless, or robot-assisted system. A robot-assisted system is the most time-efficient. Each individual electrode implantation is a standardised set of steps, starting with a small stab scalp incision, followed by making a skull drill-hole, then the fixation of a bolt in the skull, the insertion of an electrode, and lastly but not the least a meticulous dressing to minimise wound and electrode complications (Fig. 2). Post-operatively, the patient is monitored in an intensive care/ designated SEEG unit. A computerised tomography or MRI is done to confirm the location of the electrodes (Fig. 3). Overall, the complication rate of SEEG electrode implantation under a dedicated team is very low; major complications occur in 1.3 %; haemorrhage in 1 %; permanent neurological deficits in 0.6 %. It compares very favourably with subdural grid/strip implantation[5,16].

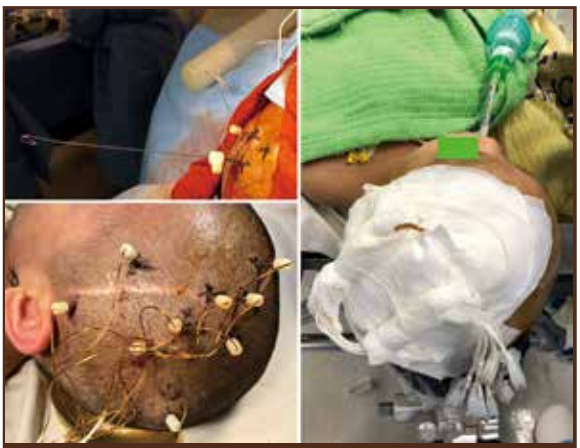

Fig. 2. Left Upper Panel: Intra-operative photo showing a skull fixation bolt has been introduced with stereotactic guidance, and a stylet inserted. Left Lower Panel: Completion of SEEG electrode implantation. Right Panel: SEEG electrodes secured with dressing. (Photos from personal collection)

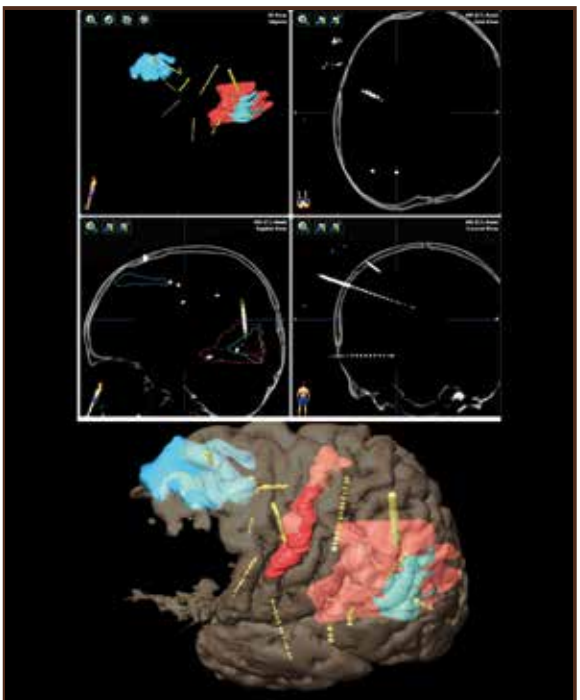

Fig. 3. Upper Panel: Bone window CT images showing SEEG electrodes. Lower Panel: 3D reconstruction image with co-registration of MRI and CT data showing the locations of SEEG electrodes in relation to the brain targets. (Photos from personal collection)

Post-implantation recording is usually completed in one week but may last up to 3 weeks[17]. Video EEG machine equipped with at least 128 channels and infrared cameras is required. Intracerebral electrical stimulation is usually performed to reproduce ictal clinical expression and to perform the functional mapping. Electrode removal is straightforward.

The SEEG recording is analysed by the electrophysiologist/neurologist with the necessary expertise, and summary findings are discussed in a multidisciplinary meeting. The SEEG data allow a 3-dimensional definition of EZ[3]. The basic analysis is by visual assessment of several typical EEG patterns of seizure onset, most commonly low voltage fast discharges. Computational/mathematical measures, such as epileptogenicity index and epileptogenicity map, have been developed based on the epileptogenic network concept to better delineate the EZ and hopefully increase the success rate of the subsequent epilepsy surgery [6].

The conclusion of a SEEG study can be confirming or disproving the initial hypothesis. When the hypothesis is confirmed, the next step is to formulate a plan for surgical resection/disconnection, or less commonly a thermo-coagulation lesioning plan. When the hypothesis is not confirmed, a second exploration i.e. a repeat SEEG may be needed with a new hypothesis, based on the SEEG findings. Overall, SEEG leads to resection or disconnection surgery in 45 -78% of patients; and over 67% of them could achieve a good seizure control, Engel 1 [15,17].

CASE ILLUSTRATION

A 10 year-old boy presented with seizure attacks (unprovoked fear, eye staring, and head turning with eye deviation to the left). A video EEG showed right middle temporal spike-and-wave epileptiform discharges. MRI of the brain showed a right lateral temporal lobe lesion with ill-defined margins, and apparently normal mesio-temporal structures (Fig. 4). He had recurrent seizure attacks despite being put on adequate dosage of levetiracetam and valproate. SEEG was performed to define the boundary of EZ and to assess whether the mesio-temporal structures can be persevered (Fig. 5). SEEG confirmed that the onset of the seizure was only from the lesion (the abnormal region on MRI); the seizure then propagated to the ipsilateral amygdala and hippocampus (Fig. 6). The patient underwent a partial right temporal lobe resection with the SEEG-defined posterior and medial boundaries, and also preservation of the mesio-temporal structures (Fig. 7). He became seizure-free after the surgery.

CONCLUSIONS

SEEG is one of the essential tools in the armamentarium of a comprehensive epilepsy surgery programme. It is a safe method and can guide subsequent resection/disconnection surgery and facilitate the achievement of good seizure control in a high percentage of a challenging subgroup of drug-resistant epilepsy patients. However, as with all tools, its value lies in the judicious and strategic deployment by its masters.

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Nurse Consultant, Department of Neurosurgery, Tuen Mun Hospital
Ms Eva TAM,
Advanced Practicing Nurse, Operating Theatre, Tuen Mun Hospital

Our sincere thanks to all of them for their efforts in setting up the SEEG Service at Tuen Mun Hospital.

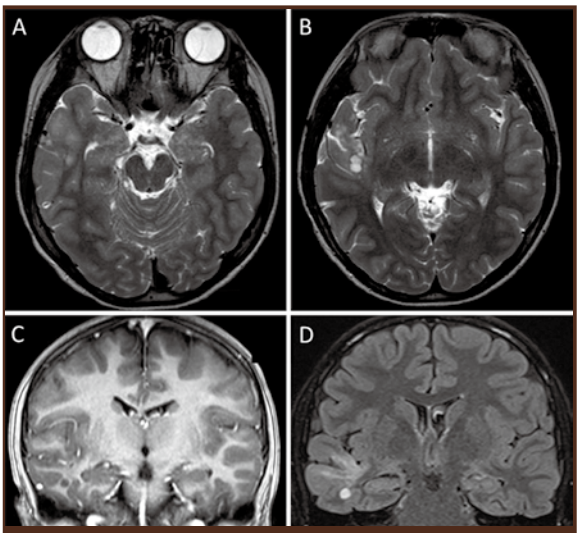

Fig. 4. Case Illustration: MRI images showing a right lateral temporal lobe lesion with ill-defined margins, and apparently normal mesio-temporal structures. A & B: Axial T2-weighted. C: Coronal T1-weighted with gadolinium injection. D: Coronal FLAIR sequence. (Photos from personal collection)

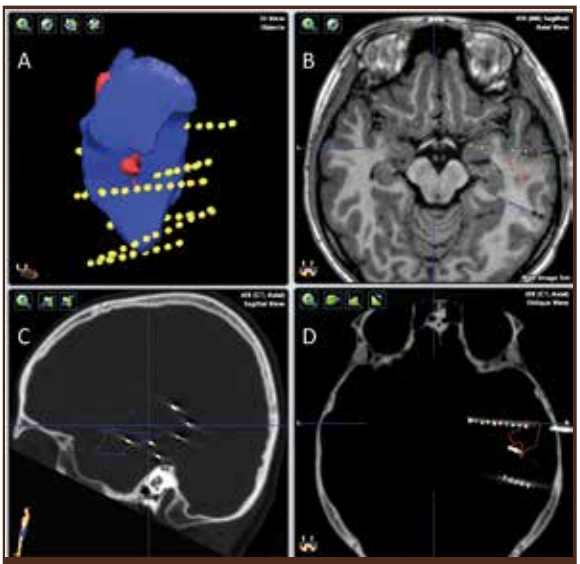

Fig. 5. Case Illustration: Images showed co-registration of MRI and CT images showing the SEEG electrodes in relation to the lesion and the mesio-temporal structures. A: 3D reconstruction. B: T1-weighted MRI with SEEG electrodes. C: Sagittal CT bone window with SEEG electrodes. D: Axial CT bone window with SEEG electrodes. (Photos from personal collection)

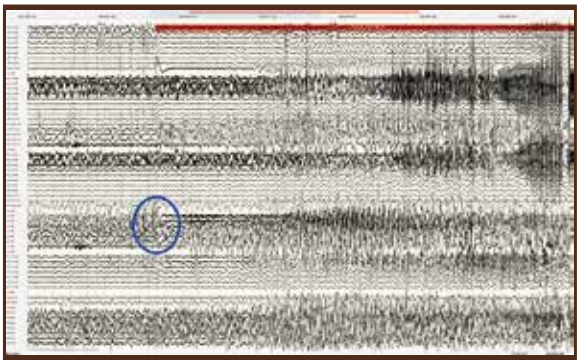

Fig. 6. Case Illustration: SEEG recording showing the onset of the seizure is from the lesion (blue circle), it then propagates to the ipsilateral amygdala and hippocampus. (Photo from personal collection)

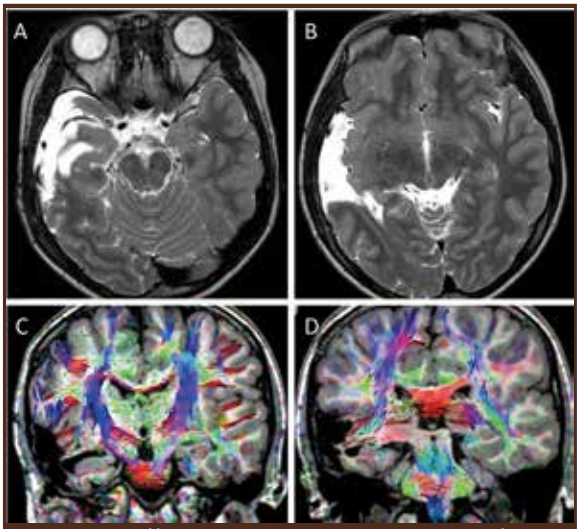

Fig. 7. Case Illustration: Post-operative MRI showing complete resection of the lesion with preservation of the mesio-temporal structures. A & B: Axial T2-weighted. C & D: Coronal T1-weighted images with diffuse tensor tractography. (Photo from personal collection)

References

1. Spencer S, Huh L. Outcomes of epilepsy surgery in adults and children. Lancet Neurol. 2008;7:525-357.
2. Jehi L. The Epileptogenic Zone: Concept and Definition. Epilepsy Curr. 2018;18:12-16.
3. Bartolomei F, Nica A, Valenti-Hirsch MP, Adam C, Denuelle M. Interpretation of SEEG recordings. Neurophysiol Clin. 2018;48:53-57.
4. Wong ST. Drug-resistant epilepsy due to focal cortical dysplasia: Surgical treatment. Hong Kong Medical Diary 2018;23(5):19-22.
5. Kovac S, Vakharia VN, Scott C, Diehl B. Invasive epilepsy surgery evaluation. Seizure. 2017;44:125-136.
6. Bartolomei F, Lagarde S, Wendling F, McGonigal A, Jirsa V, Guye M, Bénar C. Defining epileptogenic networks: Contribution of SEEG and signal analysis. Epilepsia. 2017;58:1131-1147.
7. Cardinale F, Casaceli G, Raneri F, Miller J, Lo Russo G. Implantation of Stereoelectroencephalography Electrodes: A Systematic Review. J Clin Neurophysiol. 2016;33:490-502.
8. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, Engel J, French J, Glauser TA, Mathern GW, Moshé SL, Nordli D, Plouin P, Scheffer IE. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia. 2010;51:676-685.
9. Jackson GD, Pedersen M, Harvey AS. How small can the epileptogenic region be? A case in point. Neurology. 2017;88:2017-2019.
10. Economist. An atlas of the innerverse. Economist. Feb 22, 2020 Edition
11. von Bartheld CS, Bahney J, Herculano-Houzel S. The search for true numbers of neurons and glial cells in the human brain: A review of 150 years of cell counting. J Comp Neurol. 2016;524:3865-3895.
12. Toro R, Perron M, Pike B, Richer L, Veillette S, Pausova Z, Paus T. Brain size and folding of the human cerebral cortex. Cereb Cortex. 2008;18:2352-7.
13. Isnard J, Taussig D, Bartolomei F, Bourdillon P, Catenoix H, Chassoux F, Chipaux M, Clémenceau S, Colnat-Coulbois S, Denuelle M, Derrey S, Devaux B, Dorfmüller G, Gilard V, Guenot M, Job-Chapron AS, Landré E, Lebas A, Maillard L, McGonigal A, Minotti L, Montavont A, Navarro V, Nica A, Reyns N, Scholly J, Sol JC, Szurhaj W, Trebuchon A, Tyvaert L, Valenti-Hirsch MP, Valton L, Vignal JP, Sauleau P. French guidelines on stereoelectroencephalography (SEEG). Neurophysiol Clin. 2018;48:5-13.
14. Ryvlin P, Montavont A, Ostrowsky-Coste K, Guenot M. Chapter 11. Depth electrode and stereoelectroencephalography in MRI-negative epilepsy. In MRI-Negative Epilepsy, ed. So EL, Ryvlin P. Cambridge University Press, Cambridge 2015
15. Mullin JP, Sexton D, Al-Omar S, Bingaman W, Gonzalez-Martinez J. Outcomes of Subdural Grid Electrode Monitoring in the Stereoelectroencephalography Era. World Neurosurg. 2016;89:255-258.
16. Guénot M, Lebas A, Devaux B, Colnat-Coulbois S, Dorfmuller G, McGonigal A, Reyns N, Gilard V, Derrey S, Sol JC, Clémenceau S. Surgical technique. Neurophysiol Clin. 2018;48:39-46.
17. Taussig D, Chipaux M, Lebas A, Fohlen M, Bulteau C, Ternier J, Ferrand-Sorbets S, Delalande O, Dorfmüller G. Stereo-electroencephalography (SEEG) in 65 children: an effective and safe diagnostic method for pre-surgical diagnosis, independent of age. Epileptic Disord. 2014 Sep;16(3):280-295.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
					1	2
3	4	5	* HKMA CME LIVE Dodging the Land Mines - Surgical Emergencies in Primary Care 6	* HKMA CME LIVE SGLT2 Inhibitors: What is Beyond Glucose Lowering? 7	8	9
10	11	* HKMA CME LIVE Grab Your AIR - New Approach to Asthma Management 12	* HKMA CME LIVE Breast Cancer Imaging: Ultrasound/Mammogram /MRI. Which is Better, and Why? 13	* HKMA CME LIVE Improving Dyslipidaemia Management: An Update on International Guideline and More 14	15	16
17	18	* HKMA CME LIVE Update on Hypertension Guidelines: Focus on Single-pill Combination of CCB + Diuretic 19	* HKMA CME LIVE Paediatric Vaccines 20	* HKMA CME LIVE New Era of Lipid Lowering Treatment in View of Cardiologist and Nephrologist 21	* HKMA CME LIVE Update on Management of Fatty Liver Disease 22	23
24	25	* HKMA CME LIVE Modern Paradigm in Angina Management 26	27	* HKMA CME LIVE Strategies for Better Asthma Control Among Patients 28	* HKMA CME LIVE Role of Once-daily Corticosteroids in Combined Allergic Rhinitis and Asthma Syndrome (CARAS) 29	30
31						

Date / Time	Function	Enquiry / Remarks
6 WED 2:00 PM	**HKMA CME LIVE** **Dodging the Land Mines - Surgical Emergencies in Primary Care** Organiser: HKMA-Central, Western & Southern Community Network; Speaker: Dr. TSE Tak Yin, Cyrus	Miss Antonia LEE 2527 8285 1 CME Point
7 THU 2:00 PM	**HKMA CME LIVE** **SGLT2 Inhibitors: What is Beyond Glucose Lowering?** Organiser: HKMA-HK East Community Network; Speaker: Dr. CHAN Ki Wan, Kelvin	Ms. Candice TONG 2527 8285 1 CME Point
12 TUE 2:00 PM	**HKMA CME LIVE** **Grab Your AIR - New Approach to Asthma Management** Organiser: HKMA-YTM Community Network; Speaker: Prof. WONG Wing Kin, Gary	Ms. Candice TONG 2527 8285 1 CME Point
13 WED 2:00 PM	**HKMA CME LIVE** **Breast Cancer Imaging: Ultrasound/Mammogram/MRI. Which is Better, and Why?** Organiser: HKMA-Central, Western & Southern Community Network; Speaker: Dr. WONG Chun Kuen	Miss Antonia LEE 2527 8285 1 CME Point
14 THU 2:00 PM	**HKMA CME LIVE** **Improving Dyslipidaemia Management: An Update on International Guideline and More** Organiser: HKMA-KLN East Community Network; Speaker: Dr. CHAN Kit	Miss Antonia LEE 2527 8285 1 CME Point
19 TUE 2:00 PM	**HKMA CME LIVE** **Update on Hypertension Guidelines: Focus on Single-pill Combination of CCB + Diuretic** Organiser: HKMA-KLN West Community Network; Speaker: Dr. YEUNG Kwok Kit, Lawrence	Miss Antonia LEE 2527 8285 1 CME Point
20 WED 2:00 PM	**HKMA CME LIVE** **Paediatric Vaccines** Organiser: HKMA-Central, Western & Southern Community Network; Speaker: Dr. TAM Yuen Shan	Miss Antonia LEE 2527 8285 1 CME Point
21 THU 2:00 PM	**HKMA CME LIVE** **New Era of Lipid Lowering Treatment in View of Cardiologist and Nephrologist** Organiser: HKMA-HK East Community Network; Speakers: Dr. LO Hok King, Stanley and Dr. KWOK Chun Kit, Kevin	Ms. Candice TONG 2527 8285 1 CME Point
22 FRI 2:00 PM	**HKMA CME LIVE** **Update on Management of Fatty Liver Disease** Organiser: HKMA-Shatin Community Network; Speaker: Dr. LOO Ching Kong	Ms. Candice TONG 2527 8285 1 CME Point
26 TUE 2:00 PM	**HKMA CME LIVE** **Modern Paradigm in Angina Management** Organiser: HKMA- New Territories West Community Network; Speaker: Dr. HO Kwok Tung	Miss Antonia LEE 2527 8285 1 CME Point
28 THU 2:00 PM	**HKMA CME LIVE** **Strategies for Better Asthma Control Among Patients** Organiser: HKMA-KLN East Community Network; Speaker: Dr. KWOK Yuk Lung	Miss Antonia LEE 2527 8285 1 CME Point
29 FRI 2:00 PM	**HKMA CME LIVE** **Role of Once-daily Corticosteroids in Combined Allergic Rhinitis and Asthma Syndrome (CARAS)** Organiser: HKMA-Shatin Community Network; Speaker: Dr. CHUNG Yiu Kei	Ms. Candice TONG 2527 8285 1 CME Point

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Date	Topics	Speakers
1 June, 2020	Neurogenic communication disorders (I) – Aphasia and Cognitive Communication Disorders	Dr. Anthony Pak-Hin KONG Associate Professor, School of Communication Sciences and Disorders, University of Central Florida
8 June, 2020	Communication problems in patients with Parkinson's disease	Dr. Lorinda Chen KWAN Senior Lecturer, Department of Special Education & Counseling, The Education University of Hong Kong
15 June, 2020	Dysphagia management in the elderly population	Mr. Joshua Kam-Wo MAK Speech Therapist, Private Practice
22 June, 2020	Communication problems in patients with Dementia	Ms. Rita Wai-Ming WONG Speech Therapist, Department of Otorhinolaryngology, Head and Neck Surgery, The Chinese University of Hong Kong
29 June, 2020	Neurogenic communication disorders (II) – Dysarthria and Apraxia of Speech	Mr. Raymond FONG Speech Therapist, Department of Otorhinolaryngology, Head and Neck Surgery, The Chinese University of Hong Kong
6 July, 2020	Hearing ability in the geriatric population	Ms. Polly Suk-Han LAU Senior Lecturer, Department of Special Education & Counseling, The Education University of Hong Kong

Dates : 1, 8, 15, 22, 29 June and 6 July, 2020 (Every Monday)
Time : 7:00 pm – 8:30 pm
Course Feature : Video lectures (with Q&A)
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Answers to Dermatology Quiz

Answers:

1. Pearly penile papules (PPPs)

   The main differential diagnoses are genital warts (condylomata acuminata), molluscum contagiosum and Fordyce spots (ectopic sebaceous glands).

   PPPs usually present as multiple asymptomatic small dome-shaped or filiform skin-coloured papules, arranging circumferentially in rows on coronal sulcus of glans penis. They are more common in uncircumcised males and are considered a normal variant. Histologically the findings are similar to angiofibroma. Though unrelated to sexual activity, very often they are brought to notice after men have had causal sex, causing great anxiety about STIs.

2. PPPs typically are asymptomatic and require no therapy. Reassurance about the benign nature to alleviate the anxiety of patients is often adequate. In practice, it is most important not to misdiagnose as genital warts or molluscum contagiosum, and not to treat them wrongly. Wrong labelling of STI on the patient might possibly carry medicolegal consequence.

3. PPPs per se do not require any laboratory tests. However, in view of his unprotected sex with a CSW, screening laboratory tests such as syphilis Treponema pallidum antibody test and Human immunodeficiency virus antibody test should be done. Health education about safe sex should also be given during the counselling.

Dr Lai-yin CHONG
MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)
Specialist in Dermatology & Venereology

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References :

1. L. Pradelli et al. /Clinical Nutrition 33 (2014) 785-7 92
2. Singer et al. (2009) ESPEN Guidelines on parenteral nutrition: Intensive Care. Clinical Nutrition 28: 387-400
3. Braga et al. (2009) ESPEN Guidelines on Parenteral Nutrition: Surgery. Clinical Nutrition, 28: 378-386
4. Biesalski HK. Gastroenterology 2009;137(5):92-104
http://www.espen.org/espenguidelines.html

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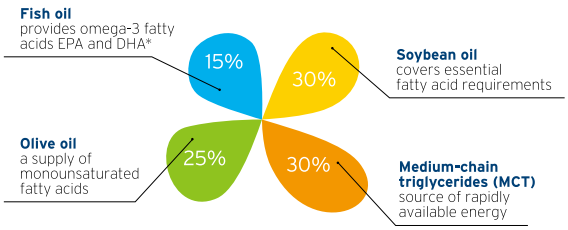

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