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EDITORIAL

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Consultant Neurologist

Editor, *Proceedings*

This is the 29th edition of Proceedings and may be my last as the sole editor, having taken on that role from Dr John Roarty AM in 1998. Fittingly, this edition is the largest to date.

I want to acknowledge that doctors and staff were universally saddened by the retirement this year of Ms Michelle Wilson as CEO of the Clinic. Michelle was always closely involved in the production of Proceedings. I am confident the new CEO, Mr Geoff Alder, will continue that involvement.

Education is one of the three guiding foundation principles of the Clinic. Proceedings, is the visible statement of that cornerstone.

The lead article by Dr Stephen Tisch (Neurologist) and colleagues describe an exciting new stereotactic approach to the treatment of certain movement disorders including essential tremor and Parkinson's disease. The treatment combines Magnetic Resonance Imaging (MRI) guidance and Ultrasound Focused Ablation to create therapeutic thermal lesions in appropriate sections of the brain without the need for open neurosurgery. On 21 November 2018, St Vincent's was the first hospital in the southern hemisphere to offer this new therapy.

Professor Jerry Greenfield, recipient of a $50,000 Foundation Grant in 2016, and Dr Samocha-Bonet have written a learned article on the mechanism of action of Metformin in management of pre-diabetes and diabetes.

Neurologists commonly see disorders of peripheral nerves and muscles with neurophysiology being the gold standard investigative tool following clinical diagnosis. MRI has proven useful as an investigation in certain inflammatory neuropathies. Peripheral nerve ultrasound is developing as a new important investigative tool, including for the common entrapment neuropathies. Dr

Dr John O'Neill

Neil Simon, Neurologist, is arguably the most experienced practitioner in the use of ultrasound for neuromuscular disease in Australia. His article describes the use of that technique in neuromuscular disease.

By careful examination of pressure pulse waveforms in the brachial artery from infancy to old age, Professor O'Rourke and colleagues have shown that apparent systolic hypertension in certain individuals (particularly tall, athletic young men) is often spurious not requiring treatment nor deserving of adverse insurance risk.

The management of prostatic cancer continues to evolve and Professor Stricker and Dr Blazevski describe focal therapy which may prove to be the preferred treatment option for that group of patients with prostatic cancer who are deemed to be at intermediate risk.

Dr Wang and Professor Omari provide an excellent review on the common problem of venous thromboembolism and in particular when mechanical filters within the inferior vena cava should be considered as part of management.

Dr Kalanie and Associate Professor Neil describe a new technique using patient custom-matched implants to enable best outcome for revision hip replacement surgery when large bony defects have developed over time after an initial hip replacement. Such exciting developments have been enabled by continued advances in bioengineering and computing.

The Medical Imaging department of St Vincent's Private and Clinic provide expert diagnostic radiological services across all subspecialties. It is now a feature of Proceedings that the department publishes three cases of particular interest which have been seen over the preceding 12 months. This article features MRI screening in breast cancer, testicular adrenal rest tumours and radiation myositis.

Finally, Dr Michael Jensen has provided a scholarly review of occupational and environmental risk factors associated with breast cancer.

The recipients of the Clinic Foundation research grants for 2019 are shown on pages 36 and 37. The total value of research grants in 2018 was $877,000 with $835,000 allocated in 2019.

Magnetic Resonance Imaging Guided Focused Ultrasound (MRgFUS): stereotactic neurosurgery without an incision

Dr Stephen Tisch

Introduction:

MRI-guided focused ultrasound (MRgFUS) has emerged as a powerful, incision-less technique that permits precise treatment of neurological disorders. Through MRI guidance, focused ultrasound beams are delivered transcranially to create small therapeutic lesions in highly specific locations within the brain. These ablations can be used to effectively treat a variety of conditions by disrupting the neural circuitry that is propagating abnormal signals.

Interest in MRgFUS is rapidly increasing due to the utility of stereotactic intervention in medically refractory movement disorders, particularly where existing surgical options remain unsuitable for patients. Advances in feasibility and safety have lead to rapid growth in clinical applications and research investigations, particularly in the field of functional neurosurgery for movement disorders. The treatment is particularly applicable to patients with tremor, and MRgFUS thalamotomy has been shown to be an effective therapy for tremor.

St Vincent's Hospital will become the first hospital in Australia and the southern hemisphere to deliver MRgFUS therapy. The $6.5 million dollar technology has been installed in St Vincent's Hospital radiology department and MRgFUS treatment for tremor patients is scheduled to commence in late 2018.

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History of Stereotactic Interventions for Movement Disorders

Surgical intervention of deep structures of the brain movement disorders and psychiatric disease has a long history since the 1950's. In particular thalamotomy and pallidotomy were effective to suppress movement disorders including tremor and dystonia by interrupting cortical, cerebellar and basal ganglia connections. Stereotactic lesions are usually created using focal heating from a radiofrequency (RF) electrode passed through the brain to the target structure. Electrical stimulation was often used to test the target area before committing to a permanent lesion, and these observations were seminal in later development of deep brain stimulation. With RF lesional surgery some patients experienced significant adverse events due to the inherent risks of passing instruments into the brain including stroke or haemorrhage and consequences of lesions encroaching nearby structures resulting in permanent neurological deficit. It was also observed that bilateral thalamotomy or pallidotomy carried a higher risk for deterioration in speech, swallowing and gait, and therefore most procedures were performed unilaterally to minimize side effects.

Dr Blake Giarola

Thalamotomy and pallidotomy declined dramatically after the advent of levodopa treatment for Parkinson's

disease in the late 1960s. The success of levodopa for Parkinson's motor symptoms was tempered by the later realization of delayed motor complications in levodopa treated Parkinson's patients including severe dyskinesia, which led to renewed interest in pallidotomy in the 1980s and brief renaissance of lesional surgery in the 1990s. Limitations of stereotactic lesions particularly side-effects associated with bilateral lesions drove interest in neurostimulation culminating in the development of modern era of deep brain stimulation (DBS) with thalamic stimulation for tremor by Alim Benabid and the Grenoble group in 1987. Studies of basal ganglia circuit dysfunction in the MPTP monkey model of Parkinson's disease elucidated the overactivity in the subthalamic nucleus (STN) as a critical node in PD pathophysiology and an efficient target for Parkinson's motor symptoms. The first Parkinson's patients were treated with STN DBS in 1993 by the Grenoble group. DBS utilizes pacemaker technology to deliver continuous high-frequency electrical stimulation through implanted electrodes to specific targets within the brain. Advantages of DBS over RF lesions include reversibility, adaptability of therapy via stimulation parameter programming and the ability to safely perform bilateral procedures to control motor symptoms on both sides of the body. Disadvantages of DBS include the need for instruments to be passed into the brain resulting in 1-2 per cent risk of intracerebral haemorrhage and stroke, and ongoing risks of infection and breakage of the implanted devices. Randomized controlled trials have shown DBS to be an effective therapy for medically refractory movement disorders including Parkinson's disease, dystonia and tremor.

Brief history of MRgFUS Technology

The therapeutic application of focused ultrasound was pioneered in the 1950's by Lindstrom and Leksell in Sweden and the Fry brothers of the University of Illinois USA. Due to the inefficiency of the ultrasound traversing bone, these procedures required an acoustic window to be provided by means of a craniotomy. In 1992 Hynynen proposed using an array of multiple focused ultrasound beams under MRI guidance to treat brain tumors, and was first to use the term MRI guided Focused Ultrasound. In 1998 Insightec an Israeli technology company partnered with GE to develop the first clinically effective, commercial MRgFUS system. The first successful clinical trials of MRgFUS were in 2003 for uterine fibroids. In 2006 Insightech achieved a major breakthrough by developing the first version of ultrasound transducer arrays capable of penetrating the skull to treat brain tissue, and being accurately focused using MRI guidance and a skull CT based algorithm. While recent advances in multi-element transducers have largely overcome skull thickness as a barrier to clinical MRgFUS, a small minority of patients have unfavourable low skull-density ratio, as determined by CT algorithm and are unsuitable for MRgFUS.

Figure 1. *Insightech Exablate 4000 system. Note hemispherical ultrasound transducer array with specialised table, allowing patient and head assembly to move in and out of the MRI bore for intra-procedural scanning and out for clinical testing of tremor.*

MRgFUS Procedural Aspects

MRgFUS utilizes multiple transducers to transmit high intensity focused ultrasound energy through the skull to ablate a precise area of brain. The machine employs two technologies: focused ultrasound beam which heats and ablates targeted tissue whilst avoiding damage to adjacent tissue not in the therapeutic target, and real-time MRI thermometry (thermal imaging sequences accurate to 0.5 degree C) to monitor the heating effect and confirm spatial accuracy of lesion placement. The currently available commercial system, Insightech Exablate 4000 uses 650 KHz high intensity ultrasound waves delivered from 1024 sources mounted in a hemispheric array **(Figure 1)** with a natural focus where the beams converge. The phase of each source can be varied, using an algorithm taking into account the predicted impedance of the overlying skull bone, such that waves summate or cancel to maximize transfer of energy across the skull. Beams traversing air filled sinuses or calcified structures such as choroid plexus are inactivated, usually leaving 80-90% of total beams available for therapy delivery. Convergent ultrasound energy is dissipated at the focal point as heating, creating a "heat spike" which is measured directly using specific MRI thermometry sequences **(Figure 2)**.

The procedure begins with the patient's head being shaved and placed in a stereotactic frame under local anaesthesia. An elastic membrane is placed over the frame and seals the head assembly with is filled with circulating chilled, degassed water in order to prevent excessive scalp heating and facilitate acoustic coupling. The natural focus is aligned with MRI localized brain target region using both mechanical adjustment of the patient's head position within the hemispherical array, and by adjusting phase of ultrasound beams to shift the position of the focal point (phase focusing). These adjustments allow the visualised heat spike to be precisely aligned with desired, MRI determined target. The delivery of MRgFUS therapy (sonication) takes place in the MRI bore with simultaneous MRI thermometry. The treatment episode comprises a series of verification sonications at 43-45°C, to determine specific energy requirements for temperature rise and verify spatial accuracy followed by focal heating at temperatures 48-50°C is assessed which

allows determination of clinical effects and side effects without inducing a permanent lesion. Clinical testing of tremor, motor symptoms and side effects is performed repeatedly after each sonication. Once the optimal lesion site is determined both radiologically and clinically the energy delivery is increased to generate focal heating 56-60°C and create a permanent stereotactic lesion. T2 MRI imaging is used to visualise the lesion post sonication and confirm correct placement.

A major advantage of MRgFUS intervention is its minimal invasive nature without requiring skin incision or skull opening. Patients remain awake, and do not require general anaesthesia. The procedure takes place in an MRI suite rather than an operating theatre and sterile fields are unnecessary. The treatment is completed in one session of 2-4 hours duration.

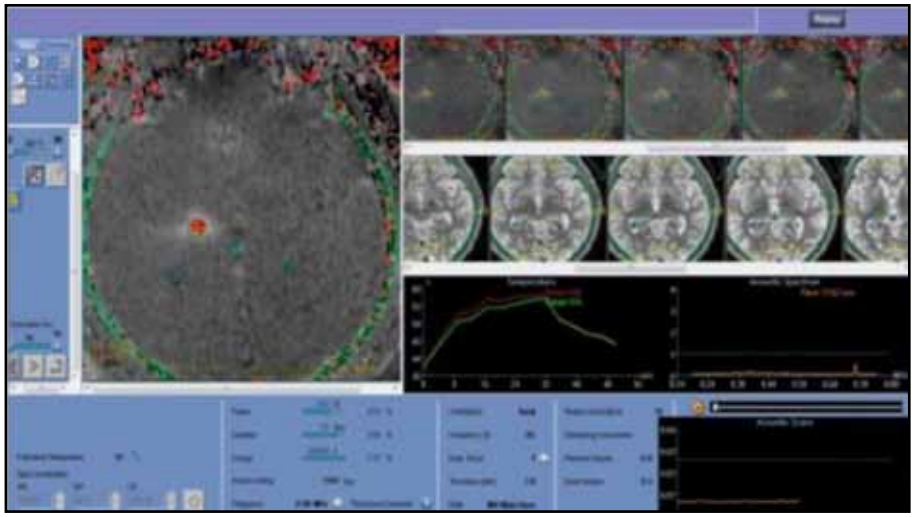
Overview of Targets and Indications:

The most well studied target for MRgFUS is the ventral intermediate (VIM) nucleus of the thalamus for tremor. Other targets within the thalamus including nucleus ventralis oralis anterior/posterior (VOA/VOP) are being investigated for treatment of focal upper limb dystonia. Basal ganglia targets, including the globus pallidus internus (GPi) for Parkinson's disease and dystonia, are being developed within clinical trials. The subthalamic nucleus (STN) has been targeted for the treatment of Parkinson's disease. An emerging development is the use of MRI diffusion tensor imaging (DTI) tractography to visualise white matter tracts connecting the cerebellum, basal ganglia and thalamus, including the dentatorubrothalamic tract and pallidothalamic tract, which are targeted directly using MRgFUS (Chazen et al 2018, Gallay et al 2018).

Essential Tremor

MRgFUS VIM thalamotomy has been shown to be effective in the treatment of essential tremor in a multicenter randomized sham controlled rater blinded study of 76 patients with 1 year follow-up (Elias et al 2016). Compared with the sham procedure MRgFUS thalamotomy resulted in 47% improvement in contralateral upper limb tremor compared with no significant change in tremor in the sham treatment group. Quality of life and disability also

Figure 2. *MRI thermometry provides real time MRI thermal brain imaging during MRgFUS sonication. Note thermal image of thalamic target during sonication and real-time heating curve showing temperature.*



improved significantly only in the active MRgFUS group. Benefits for tremor were maintained at 12 months. Side effects were most commonly transient parasthaesias and gait unsteadiness, with only one patient experiencing a severe adverse event, persistent numbness in one hand. On the basis of this study, MRgFUS was granted FDA approval for treatment of essential tremor in 2016 and Australian TGA approval was granted in 2017. An extension study following the same cohort has shown stable improvement in tremor to two years follow up (Chang et al 2017). A recent study evaluated the safety and side effect profile of MRgFUS thalamotomy in 186 patients from five studies. Procedure-related serious adverse events were very infrequent (1.6 per cent), with no intracerebral hemorrhages or infections. Adverse events were usually transient and were commonly rated as mild (79 per cent) and rarely severe (1 per cent). As previously reported, abnormalities in sensation and balance were the commonest thalamotomy-related adverse events. (Fishman et al 2018)

Parkinson's Disease

Studies have reported beneficial effects of MRgFUS VIM thalamotomy for treatment of Parkinson's tremor (Bond et al 2017, Zaaroor et al 2018) with improvement in tremor of up to 60 per cent. MRgFUS pallidotomy has also been reported beneficial for cardinal motor symptoms of rigidity and bradykinesia and relief of dyskinesia (Jung et al 2018). Unilateral subthalamic nucleotomy using MRgFUS has been shown to be beneficial in reducing Parkinson's motor symptoms by approximately 50 per cent in both ON and OFF dopaminergic medication state, with one patient experiencing upper limb dyskinesia (hemichorea/hemiballism) contralateral to the subthalamic lesion, which resolved within three months (Martinez-Fernandez et 2018).

Dystonic Tremor and Dystonia

Dystonic tremor may closely resemble and be misdiagnosed as essential tremor. It typically produces a jerky tremor of hands and head, worse in certain positions or with particular tasks. A recent study reported beneficial effects of MRgFUS VIM thalamotomy in three patients with dystonic tremor (Fasano et al 2017). MRgFUS thalamotomy targeting VOA/VOP is being studied as a treatment for focal upper limb dystonia in Japan (Horisawa et al 2018), where conventional RF thalamotomy of VOA/VOP is an established treatment for focal upper limb dystonia including writer's cramp and musician's dystonia.

Other Emerging Clinical Applications for MRgFUS

There is burgeoning research into the use of MRgFUS for the ablative treatment of brain tumours, epilepsy, psychiatric disorders such as obsessive compulsive disorder and pain. Neuropathic pain was actually the first brain condition treated successfully using MRgFUS using medial thalamotomy (Martin et al 2009).

MRgFUS can also be used to disrupt the blood-brain barrier (BBB) for targeted medication delivery of chemotherapy, antibiotics, immunological agents or neurotrophic growth factors. Reversible BBB disruption can be facilitated by injection of micro-bubbles into the circulation which oscillate, stretching the vessel wall, and gadolinium enhanced MRI can be used to monitor the area of BBB disruption (Weintraub et al 2017). MRgFUS can also be used to ultrasonically disperse insoluble protein aggregates in the brain such as amyloid and tau, and is being investigated as potential therapy for Alzheimer's disease (Meng et al 2017). Additionally, focused ultrasound offers the possibility of reversible neuromodulation by using the mechanical and non-thermal properties of low-intensity acoustic energy (Fomenko et al 2018). The reversible effect at low temperature allows for therapeutic testing while creating lesions using MRgFUS. The ability to modulate neuronal activity with high spatial resolution may soon be applied clinically and offers great potential in elucidating brain networks.

Comparison of MRgFUS with Current Therapies and Safety Considerations

MRgFUS ablative therapy aims to provide immediate improvement of symptoms. Real-time feedback and monitoring allows refinement of the target site and focused therapeutic dosing. It also has a high safety profile with minimal complications. There currently remains no randomized head-to-head studies directly comparing DBS and MRgFUS but there are several studies that have compared the therapies using the available data which have concluded that MRgFUS thalamotomy for tremor provides therapy benefits equivalent to conventional RF thalamotomy or thalamic DBS (Kim et al 2017).

From a safety perspective, MRgFUS eliminates the need for skin incision, skull opening or instruments being passed into the brain. This greatly reduces the risk of intracerebral haemorrhage or stroke, which have so far not been reported (Fishman et al 2018, Gallay et al 2018). MRgFUS is associated with a relatively frequent incidence of mild transient side affects, in particular parasthaesiae following MRgFUS thalamotomy. MRgFUS can be considered minimally invasive by virtue of its novel transcranial delivery system however a small permanent brain lesion mediates the therapeutic effects. Precise placement of MRgFUS lesions is critical to the success of MRgFUS therapy and conversely misplaced lesions have potential to result in permanent neurological deficit. Given the criticality of correct lesion placement for safety, it is reassuring that the available evidence suggests the MRgFUS is very accurate. A recent study of 180 MRgFUS treatments found the mean lesion location 3D accuracy was 0.73 ± 0.39 mm to the intended target (Gallay et al 2018). MRgFUS also minimizes infection and bleeding and has a shorter recovery time. The patient does not require general anaesthetic and does not experience hardware complications or require programming of device therapy. Procedural times and expense are less than for DBS and despite high establishment costs, the technology may provide a more affordable option in resource deficient countries.

Conclusions and Perspectives

MRgFUS has emerged as a novel, noninvasive alternative to conventional neurosurgery for treatment of a number of brain disorders. As a feasible method for precision ablation in deep brain structures it provides immediate and sustained improvement in tremor and has great potential to be equally effective in other movement disorders. It does not involve implantation of instruments or devices, does not require laborious postoperative adjustments or replacements, has no risk of infection and is more economical than deep brain stimulation. As stereotactic lesions enjoy a renaissance, MRgFUS is increasingly the preferred methodology. Neither lesions nor neurostimulation guarantees therapeutic control or represent a cure for underlying brain disorders, particularly patients with chronic neurodegenerative conditions who continue to deteriorate. Nevertheless, MRgFUS provides a new way to significantly improve quality of life for patients with movement disorders and potentially other neurological conditions in the future.

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Dr Jerry Greenfield
Dr Dorit Samoche-Bonet

Prevention and treatment of type 2 diabetes with metformin – the importance of liver insulin resistance and gastrointestinal microbial dysbiosis

Dr Jerry Greenfield

Dr Dorit Samocha-Bonet

Prediabetes is a state of dysglycaemia preceding type 2 diabetes (T2D). It is a risk factor for macro- and micro-vascular disease, fatty liver, cognitive dysfunction and cancer.[1] The prevalence of prediabetes depends on the definition used to diagnose it and on the population studied. The rate of prediabetes in Australian adults, although not recently reported, is expected to be similar to the 38% rate recently reported in American adults.[2] While not everyone with prediabetes will develop T2D, the annual rate of progression from prediabetes to T2D is high. In the US Diabetes Prevention Program Outcomes Study (DPPOS), the annual progression rate was 11%,[3] and in a population of Asian Indians with impaired fasting glucose or impaired glucose tolerance (IFG and IGT, respectively, Box 1) at baseline it was 13.4%.[4]

Recent post-hoc analysis of the Diabetes Prevention Program (DPP) data[5] demonstrates that despite early intervention in prediabetes with the first-line T2D medication metformin, a surprisingly large proportion of patients progressed to T2D. Metformin is an ideal medication to initiate for diabetes prevention due to its excellent safety profile (lack of hypoglycaemia), marginally beneficial effect on body weight, modest evidence of cardio-protection[6] and low cost. However, numerous studies suggest a wide variability in glycaemic response to metformin, and non-response is common.[7]

Randomised clinical trials suggest that metformin monotherapy fails to achieve glycaemic control in a large proportion of people with T2D. For example, in a double-blind, randomised, controlled clinical trial of >4000 individuals with newly diagnosed T2D, Kahn and colleagues reported that a cumulative rate of 21% of patients failed to reach fasting plasma glucose (FPG) ≤10 mmol/L during 5 years of metformin monotherapy.[8] Similarly, in a sub-cohort of the Genetics of Diabetes and Audit Research Tayside Study (GoDARTS),

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49% of metformin-treated patients failed to achieve HbA1c ≤7% (53 mmol/mol) within 1 year from treatment initiation,[9] despite good adherence. Early metformin intervention in prediabetes has been trialled in the DPP[10] and DPPOS[3] with the primary outcome being T2D diagnosis. On average, metformin treatment prevented 31% and 18% of T2D cases relative to placebo, at 3 and 15 years of treatment, respectively.[11] Notably, large variability in T2D risk reduction with metformin has been documented,[11] with 21% of metformin adherent participants developing T2D at 3 years.[5] Categorical analysis of better- and worse- glycaemic responders to metformin provides conflicting characteristics of better responders. In one post-hoc analysis of the DPP data, younger individuals with elevated BMI and FPG responded better,[11] while a separate analysis suggested that older age, smoking, history of polycystic ovarian syndrome, family history of T2D, elevated FPG and serum triglycerides predicted greater risk of progression to T2D.[5] In summary, poor response to metformin in prediabetes and T2D is not uncommon, and the clinical predictors of better and worse response remain unclear.

While the mode of action of metformin is still being investigated, the liver and the gastrointestinal tract are thought to be the primary targets responsible for the improvement in glycaemia. Metformin has been suggested to improve liver insulin resistance[12] and to correct gastrointestinal microbial dysbiosis,[13] an established pathophysiology described in patients with dysglycaemia.[14]

Findings from our studies, using gold-standard tools to characterise whole body glucose regulation suggest that prediabetes is made up of diverse phenotypes.[15-17] We have found that while some people present with insulin resistance in both muscle and liver, others exhibit insulin resistance in muscle and maintain insulin sensitivity in the liver.[15] Normal liver insulin sensitivity may be one reason individuals have a poor glycaemic response to metformin.

The liver and the gastrointestinal tract are thought to be the main targets responsible for improvement in glycaemia in patients treated with metformin. Studies in patients with T2D using hyperinsulinaemic-euglycaemic clamps with stable glucose isotopes suggest that metformin acts to reduce liver insulin resistance, as measured by lower endogenous glucose production (EGP).[12] Insulin-mediated tissue glucose disposal, primarily by muscle, was not affected directly by metformin.[18] To-date, no study has tested whether liver insulin resistance is obligatory for effective metformin treatment.

Prediabetes: Fasting plasma glucose (FPG) 5.6-6.9 mmol/L (impaired fasting glucose, IFG) or 2-h plasma glucose during 75-g oral glucose tolerance test (OGTT) 7.8-11.0 mmol/L (impaired glucose tolerance, IGT) or haemoglobin A1c (HbA1c) 5.7-6.4% (39-47 mmol/mol) in participants without a prior diabetes diagnosis.

Normal glucose tolerance (NGT): FPG <5.6 mmol/L and 2-h plasma glucose during 75-g OGTT <7.8 mmol/L and HbA1c <5.7% (39 mmol/mol).

Table 1: *Glucose tolerance definitions*

A growing body of evidence suggests that the gut microbiota play a role in whole body glucose regulation. Alterations in microbial composition, termed dysbiosis, have been described in prediabetes and T2D. In particular, depletion of butyrate-producing bacteria may be an early marker of T2D,[19-22] and enrichment of opportunistic pathogens[19] and species with increased capacity for energy harvest from the diet[23] have been described. Circulating metabolites, including amino acids, short-chain fatty acids and vitamins originating from the microbial community inhabiting the gastrointestinal tract serve as active messengers and may have a profound effect on the immune system[24] and on insulin sensitivity.[25]

Two recent studies in rodents[26,27] provide evidence for a direct involvement of metformin in mediating improved glycaemia through alterations in the gut microbial taxa. Faecal microbiota transplant (FMT) donated by 4-month metformin (1700 mg/d)-treated patients with T2D improved glucose intolerance (measured by intraperitoneal glucose tolerance test) in germ-free mice.[26] Relative abundance (RA) of more than 80 bacterial strains changed in all 22 subjects treated with metformin vs only one of 18 treated with placebo. Changes were primarily identified in the ❑-proteobacteria (e.g., *Escherichia coli*) and *Firmicutes*. At the genera level, *Escherichia*, *Bifidobacterium* and *Akkermansia muciniphila* increased and *Intestinibacter* decreased. A co-abundance network analysis revealed that 2-month metformin treatment increased the number of positive connections among microbial genera, especially between short-chain fatty acids-producing genera.[26] Different alterations were reported in the upper small intestine microbial RAs in high fat fed rats treated with FMT donated by rats treated with metformin infused into the upper small intestine for 3 days.[27] EGP decreased in the rat hosts while upper small intestine Lactobacillus RA increased.[27] The improvement in EGP was attributed to increased glucose sensing in the upper small intestine mediated by sodium glucose cotransporter (SGLT)-1.[27]

In summary, the response to metformin in preventing and treating type 2 diabetes may be determined by the presence of hepatic insulin resistance and may be mediated via alterations in the microbiomic signature of the host. Further studies are required to test these hypotheses. Personalised treatment approaches to T2D require elucidation of the predictors of effectiveness of individual diabetes treatments.

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Dr Neil Simon

Nerve and muscle ultrasound in the neurophysiology clinic

Dr Neil Simon

Medical students are taught that diagnoses are confirmed by obtaining a detailed history and examination. Investigations confirm what is suspected clinically. This remains true in neuromuscular medicine.

Neurophysiology has long been considered an extension of the clinical examination in neuromuscular medicine (perhaps so as not to contradict the above adage). The advent of high frequency ultrasound probes that have the ability to outline even small peripheral nerves and define normal and pathological muscle tissue has brought ultrasound to the forefront of the diagnostic process in neuromuscular medicine. Like neurophysiology, bedside nerve and muscle ultrasound may also be considered an extension of the neurological examination, as it provides useful anatomic information.

Peripheral Nerve Ultrasound

Normal peripheral nerve has a 'honeycomb' appearance on ultrasound studies, with hypoechoic (dark) fascicles surrounded by hyperechoic (light) perineurium and epineurium **(Figure 1)**. There is some variation in the ultrasound appearance of normal nerves. For example, the typical fascicular pattern may not be evident in more proximal nerves such as the brachial plexus.

Ultrasound demonstrates characteristic features of peripheral nerve injury. An injured nerve becomes larger.

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An injured nerve loses its internal fascicular architecture and becomes more hypoechoic. There may be increased nerve vascularity detected by Doppler imaging in some nerve injuries while vascular flow is not usually detected in normal peripheral nerve.

Ultrasound may provide additional information to assist the diagnosis of peripheral nerve injury. There may be abnormal nerve mobility. This may be either abnormally restricted mobility, such as may be seen in carpal tunnel syndrome. Alternatively, there may be abnormally increased nerve mobility such as ulnar nerve subluxation across the medial epicondyle in ulnar neuropathy. Anomalous and abnormal anatomic structures may be identified as contributors to the nerve injury.

Clinical Applications Of Nerve Ultrasound

Imaging in compressive neuropathies

A core goal of diagnosis of compressive neuropathy is to localise the nerve lesion. Neurophysiological studies have traditionally been employed for this purpose however, the sensitivity of neurophysiological studies varies depending on the disorder being evaluated and even carefully performed neurophysiology studies may provide only non-localising information. Detailed neurophysiological studies in carpal tunnel syndrome are up to 90% sensitive. Approximately 50% of patients with carpal tunnel syndrome but normal neurophysiology studies will demonstrate abnormalities of the median nerve at the wrist on ultrasound. For ulnar neuropathy at the elbow, the localising sensitivity of neurophysiology is lower (approximately 70%) and increases to about 85% with the addition of ultrasound. Higher sensitivity still is obtained by adding in MRI studies.

Many consider entrapment neuropathy to be synonymous with compressive neuropathy. However, this is not the case. Most compressive neuropathies are not caused by entrapment of the nerve by a normal, aberrant or pathological intrinsic structure. Carpal tunnel syndrome is almost always caused by nerve entrapment. However, only approximately 25% of ulnar neuropathy at the elbow is caused by true entrapment of the nerve (with the remainder caused by extrinsic compression of the nerve or traction of the nerve across the elbow) (Omejec and Podnar, 2016). True entrapment of the peroneal nerve in the fibular tunnel is a rare cause of peroneal neuropathy (Stewart, 2008).

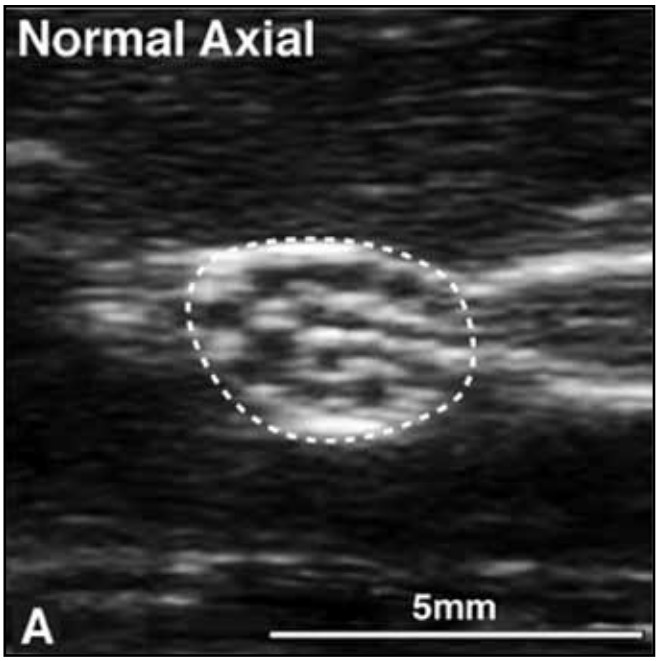

Figure 1 – *Axial ultrasound image of a normal nerve demonstrating the typical fascicular pattern.*

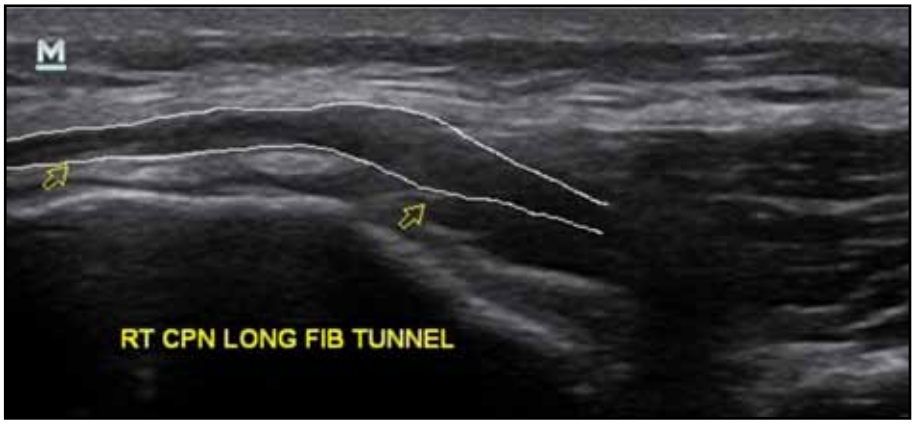

Figure 2 – *True entrapment of the peroneal nerve. A 25 year old male presented with a one week history of peroneal neuropathy with no precipitant. Ultrasound showed focal enlargment of the nerve just proximal to the entry of the fibular tunnel with sharp transition of nerve caliber back to normal within the fibular tunnel.*

Identifying true entrapment is critical as this will help determine treatment. For example, if there is a significant symptomatic compressive neuropathy caused by entrapment of the nerve within the limb, then surgical release of the nerve from the entrapping structure should be a management priority. However, if there is no evidence of entrapment, and findings suggest that the nerve injury is caused by extrinsic pressure, the rationale for surgical intervention becomes more tenuous.

As an illustration of the above point, consider treatment of two common compressive neuropathies, carpal tunnel syndrome and ulnar neuropathy at the elbow. Carpal tunnel syndrome responds very well and similarly to targeted corticosteroid injection or surgical decompression. Following corticosteroid injection, nerve swelling and vascularity reduces, and this presumably diminished the entrapment in the carpal tunnel. The effects of the corticosteroid are temporary and the symptoms of carpal tunnel syndrome typically recur after about 3-6 months. Surgical decompression of the transverse carpal ligament usually results in resolution of compression related symptoms (nocturnal and positional pain, tingling and numbness) although features of established axonal injury such as permanent numbness and weakness may remain.

Conversely, ulnar neuropathy at the elbow does not respond to corticosteroid injection. One could propose that the relatively low rate of true entrapment in ulnar neuropathy at the elbow may explain the discrepancy in treatment response when compared to carpal tunnel syndrome (Podnar and Omejec, 2016). In addition, while surgical decompression of the ulnar nerve at the elbow has been

shown to improve symptoms, so have conservative measures such as education and splinting. Of paramount importance, there have never been any surgical trials in ulnar neuropathy at the elbow with a control treatment arm, rendering the evidence guiding the treatment of ulnar neuropathy at the elbow of low quality (Simon, 2018).

Nerve ultrasound is able to identify features of nerve entrapment, which is demonstrated by a focal stricture of the nerve at the site of the entrapping structure **(Figure 2)**. As such, nerve ultrasound is invaluable in providing an evidence-based treatment plan.

There are also specific instances when patients should be screened for anatomic abnormalities with imaging. Patients presenting with strictly unilateral carpal tunnel syndrome with significant clinical or neurophysiological abnormalities should be screened for a ganglion cyst contributing to nerve compression. Patients presenting with peroneal neuropathy without a clear precipitant should be screened for intraneurial ganglion cysts (Spinner et al. , 2007). Patients with unusual or atypical peripheral nerve syndromes should be screened for intrinsic nerve abnormalities or aberrant anatomy.

Imaging in peripheral neuropathy

There are a variety of abnormalities that may be detected on ultrasound in neuropathy (Gallardo et al. , 2015). A diseased nerve may become enlarged, may demonstrate altered fascicular appearances or increased perifascicular connective tissue or may occasionally become smaller. Although counterintuitive, axonal neuropathy is only occasionally associated with reduction in nerve calibre. Diabetic neuropathy often shows mild nerve enlargement.

Accordingly, nerve ultrasound has a relatively limited role in the work-up of a typical axonal peripheral neuropathy. However, ultrasound can refine the diagnosis in patients presenting with demyelinating neuropathy. In particular ultrasound identifies characteristic changes in hereditary and acquired demyelinating neuropathies and may be useful to distinguish the two where the diagnosis is unclear.

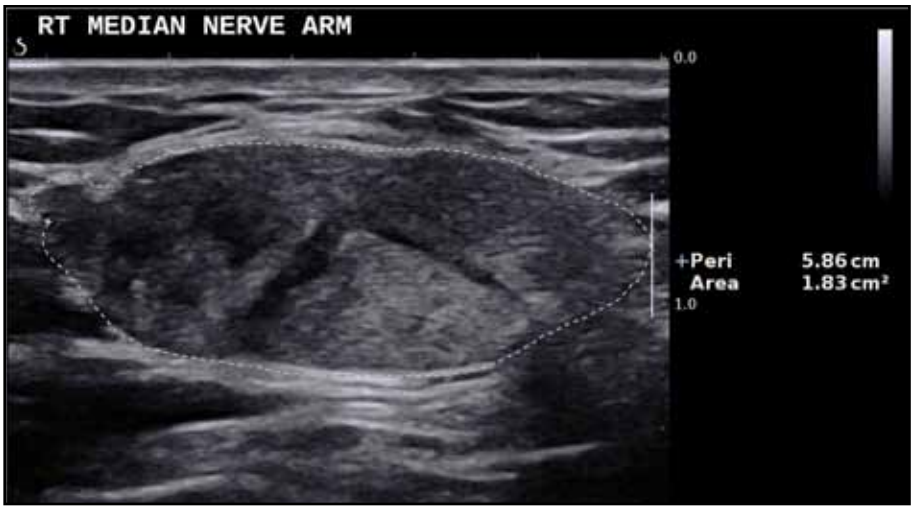

Figure 3 – *Nerve enlargement in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Massive nerve enlargement is seen in the proximal median nerve (183mm2 versus normal value of approximately 15mm2). There are several enlarged hyperechoic fascicles.*

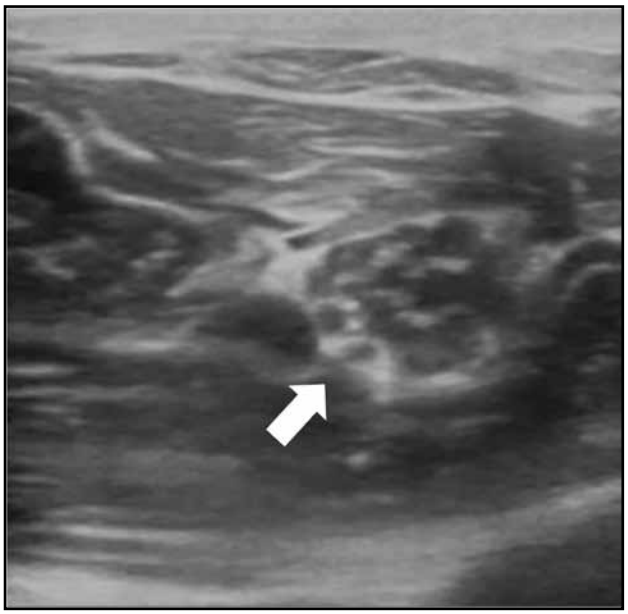

Figure 4 – *Homogenous nerve enlargement in Charcot-Marie-Tooth Type 1A.*

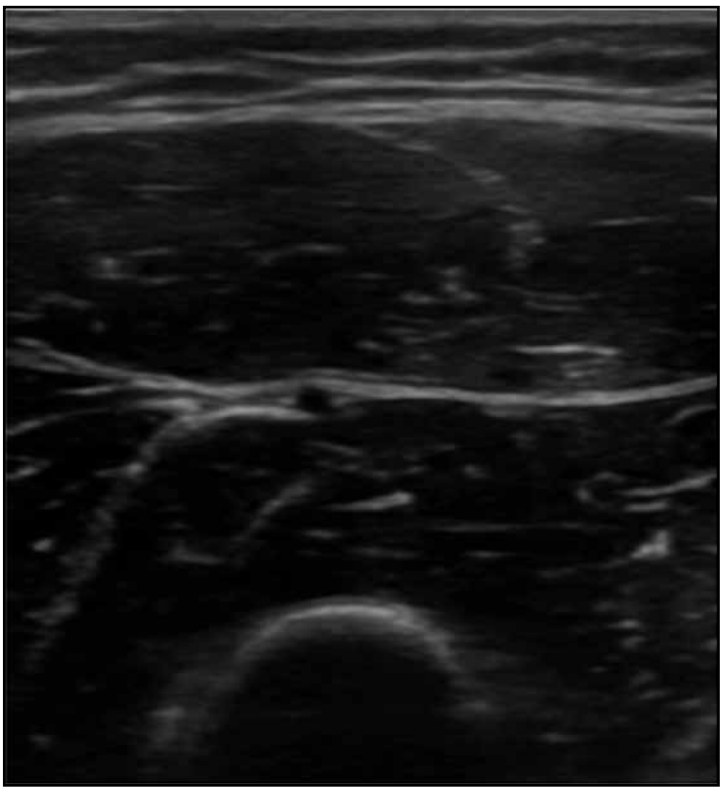

Figure 5 – *Ultrasound of normal quadriceps muscle showing a 'starry night' pattern.*

The commonest form of Charcot-Marie-Tooth disease (CMT), CMT1A is associated with diffuse and homogenous nerve enlargement. Other subtypes of CMT have less consistent nerve abnormalities. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) may be associated with nerve enlargement but this often shows within nerve and between nerve variability, in contrast to CMT **(Figures 3 and 4)**.

Muscle Ultrasound

Normal muscle demonstrates a 'starry night' pattern on ultrasound with predominantly hypoechoic muscle interspersed with small hyperechoic foci corresponding to connective and neurovascular tissue **(Figure 5)**. In both myopathy and neurogenic muscle injury muscles become smaller. In myopathy, infiltration of fat and muscle and variation in muscle fibre size results in a ground glass appearance on ultrasound with homogenously increased echogenicity **(Figure 6)**. In neurogenic muscle injury ultrasound demonstrates a more patchy and streaky appearance **(Figure 7)**. Muscle ultrasound features evolve with the time course of denervation and reinnervation changes (Simon et al. , 2016).

Muscle ultrasound can be useful in a number of ways. Ultrasound may identify abnormalities where EMG may not. EMG is of notoriously low sensitivity in myositis due to the patchy nature of the disease. Imaging (with either ultrasound or MRI) may identify a suitable target for muscle biopsy.

Ultrasound may identify characteristic patterns of muscle disease, which may clarify a diagnosis and rationalize the investigative process. For example, inclusion body myositis is characterised by predominant involvement of flexor digitorum profundus relative to the overlying flexor carpi ulnaris **(Figure 8)** (Noto et al. , 2014). Patients with congenital myopathy related to mutation in the Collagen VI gene (such as Bethlem and Ullrich myopathy) demonstrate a pathognomonic central cloud in rectus femoris, due to the predilection of the disease for fascial components of the muscle **(Figure 9)**.

Ultrasound also has the ability to identify normal and abnormal

Figure 6 – *Ultrasound of quadriceps in a patient with severe muscular dystrophy.*

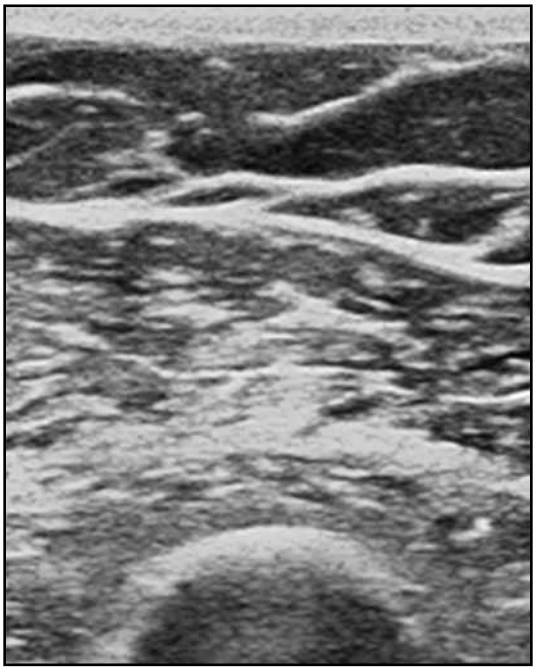

Figure 7 – *Ultrasound of biceps in a patient with amyotrophic lateral sclerosis showing severe neurogenic changes.*

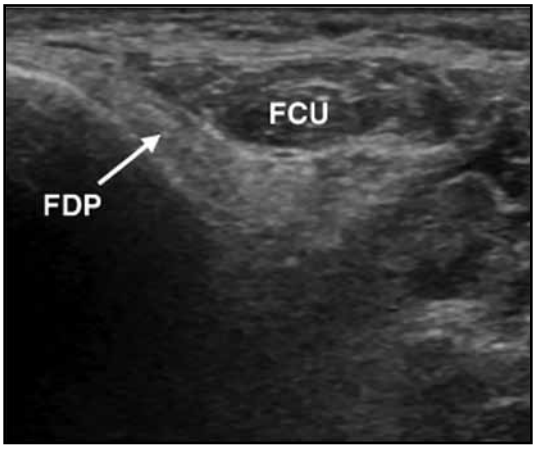

Figure 8 – *Ultrasound of the forearm in a patient with inclusion body myositis demonstrating greater abnormalities in flexor digitorum profundus (FDP) relative to flexor carpi ulnaris (FCU).*

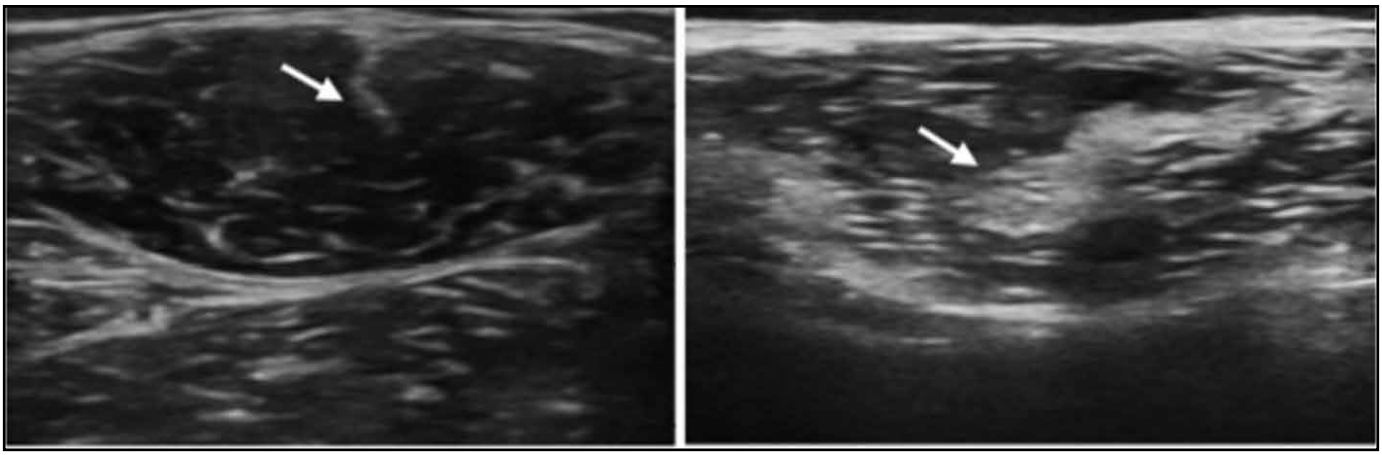

Figure 9 – *Ultrasound of rectus femoris in a normal individual (left) and a patient with Bethlem myopathy (right). Note the central fascial insertion (arrow) which is thin in the normal muscle and abnormally thickened in Bethlem myopathy.*

movements of muscle. Fasciculations are evident as brief twisting movements within the muscle and are readily distinguished from other movements. Ultrasound improves the detection of fasciculations relative to EMG. Ultrasound can distinguish amyotrophic lateral sclerosis from benign peripheral nerve excitability diorders (Noto et al. , 2018). As such, it is a valuable supplement to the work up of patients with suspected motor neurone disease.

Finally, the ability to detect normal muscle movement has useful roles in the neuromuscular clinic. Perhaps the best example is for the assessment of the diaphragm (Simon and Kiernan, 2015). Ultrasound can identify normal diaphragmatic thickening with respiration. Chronic neurogenic or myopathic diaphragmatic disorders result in a thin diaphragm that does not thicken with inspiration. Acute phrenic neuropathy results in a diaphragm of normal thickness, but which does not thicken with inspiration. Ultrasound studies are also useful to plan EMG Of the diaphragm, as having an estimate of depth and thickness of the diaphragm prior to the EMG procedure can reduce the risk of inadvertent injury such as pneumothorax.

Conclusions

Ultrasound of nerve and muscle is relatively cheap and can be performed within the clinic at the time of other assessments. Ultrasound assessment of nerve and muscle is an indispensible part of the work up of neuromuscular disorders and will soon pervade all major hospital departments and clinics. A suitably trained neurologist is the optimal person to be performing nerve and muscle ultrasound studies as they can integrate the anatomic findings provided by the ultrasound with the clinical and neurophysiological (functional) data already obtained. In some instances, ultrasound studies provide information that enriches the diagnosis and potentially streamline subsequent investigation. In other instances, ultrasound provides information critical to planning suitable management of the presenting complaint. An in-clinic multimodality assessment of neuromuscular disease is the future of this neurology subspecialty.

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Spurious Systolic Hypertension of Youth

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Almost 20 years ago, with Ray Kelly and others, our group published an article entitled "Spurious Systolic Hypertension of Youth" in a journal "Vascular Medicine", newly launched by Victor Dzau, then Head of the Cardiovascular Division of Harvard's Brigham and Women's Hospital in Boston.

This article described a group of young men with persistently elevated brachial cuff SP, but with no other evidence of hypertension or target organ disease, and with normal cuff Diastolic Pressure (DP). These subjects showed high narrow peaks in their radial artery pressure wave tracings recorded non-invasively and had normal mean pressure. We attributed the apparently high brachial SP readings to exaggeration of high frequency components of the aortic pressure wave, and so to distortion of the pulse during travel down the arm from the ascending aorta to brachial and radial sites. We confirmed the phenomenon by recording the pulse waves simultaneously, invasively and non-invasively, in patients undergoing cardiac catheterisation. We considered the condition to be a normal variant, and not to warrant treatment. In follow up over 20 years none of these persons were known to develop vascular disease, and brachial SP shifted into the normal range.

Our views however were and still are contentious. Large US studies including the Systolic Hypertension in the Elderly Project (SHEP) confirmed the high mortality of persons with elevated SP (> 140 mmHg) over the age of 60 years, and the benefits of treating such persons towards a goal SP of 130 mmHg. SHEP had great influence on medical practice around the world, and it became standard practice to treat high SP on the basis of SHEP, irrespective of age.

However, other anomalies in the classic epidemiological and life insurance observations were noted. For cuff BP, the Framingham study had shown that under age 40, brachial cuff DP was the best predictor of morbidity and mortality while brachial cuff SP was the best predictor over age 50 years. In persons over age 60 years, brachial SP, while independently predictive of cardiovascular events, became inversely related to DP, so that the best predictor of events was brachial cuff Pulse Pressure (PP), i.e. SP minus DP at this time of life.

Reconciliation and interpretation of all this information was very difficult. Our own approach in Ray Kelly's

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absence (he had died of renal cancer in 2000) was to look back at his work on amplification of the pulse wave in the upper limb and to consider what we could achieve if we used our methods of Pulse Wave Analysis (PWA) to see what happens to the proximal aortic pressure wave, (especially peak central SP) and central PP throughout life.

We approached such analysis by considering patterns of brachial cuff SP change in well accepted US adult and children's epidemiological studies – Framingham for adults, the National High Blood Pressure Education Program (NHBPEP) for children (figure 1). This brought to light two phenomena of which we were not initially aware – first, the youngest age in the Framingham cohort was 25 years, and the oldest age for the paediatric group was 18 years; there was a gap (no data) for normal values in this critical age range when adult life begins and people first enter the work force. We found just one (European) study to fill this gap (black line in figure 1, covering 10 to 35 years). The second phenomenon was that there appeared to be a plateau of brachial SP change with age between 18 to 30 years for both males and females **(Figure 1)**, before the course of brachial cuff SP versus age headed up again to age 70 years and beyond. Cuff SP levels were similar for males and females up to around age 15, whereafter male levels of brachial SP were higher than female. This plateau phenomenon was subsequently shown over the same young adult range 18 – 30 years in other European and Australian National Heart Foundation studies.

Figure 2 shows an example of a young man with "spurious systolic hypertension" where brachial cuff BP was 154/78, and calculated central systolic pressure was 127/81. We used a US Food and Drug Administration-validated generalised transfer function on the radial pulse waveforms to correct for pressure wave distortion in the arm, and generate central pressure. Such waveforms of course were not available for the initial Framingham study, but were available in a similar study undertaken by our colleagues from University of Cambridge UK, which had similar changes in brachial cuff SP with age as in Framingham (figure 1). Our colleagues had generated the central aortic waveforms in this Cambridge cohort, using our (the same) generalised

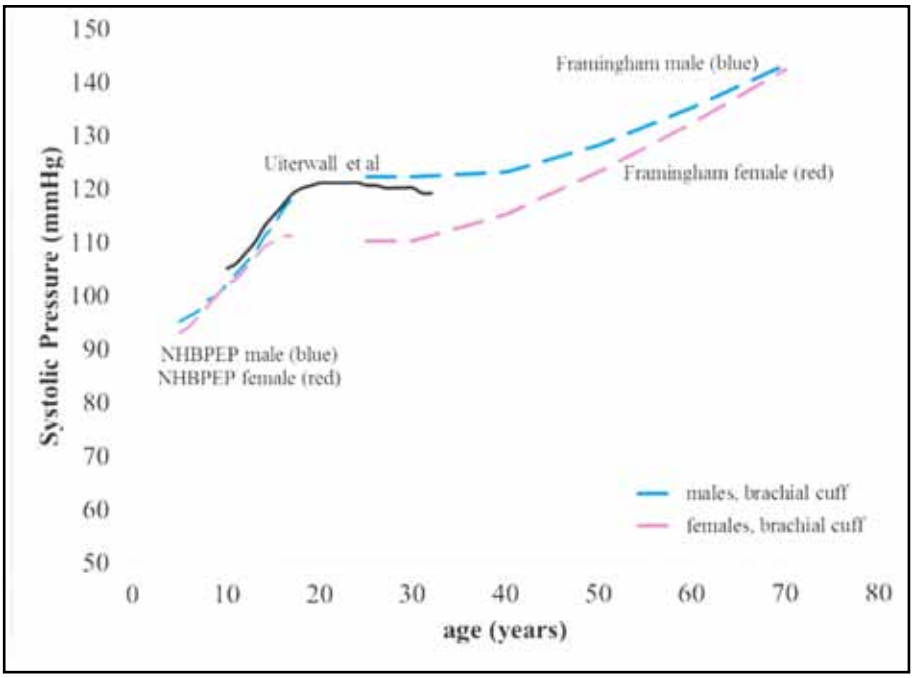

Figure 1. *Changes in cuff brachial SP in males (light blue dashed line) and in females (pink dashed line) in the Framingham study between 25 and 70 years of age. This is complemented by data from the National High Blood Pressure Education Program (NHBPEP) for children between and 5 and 18 years with light blue dashed lines for boys and pink dashed lines for girls. There is a gap of 7 years between the 2 studies, which is filled in by data of Uiterwaal et al from the Netherlands on children studied yearly from 10 to 35 years (black line).*

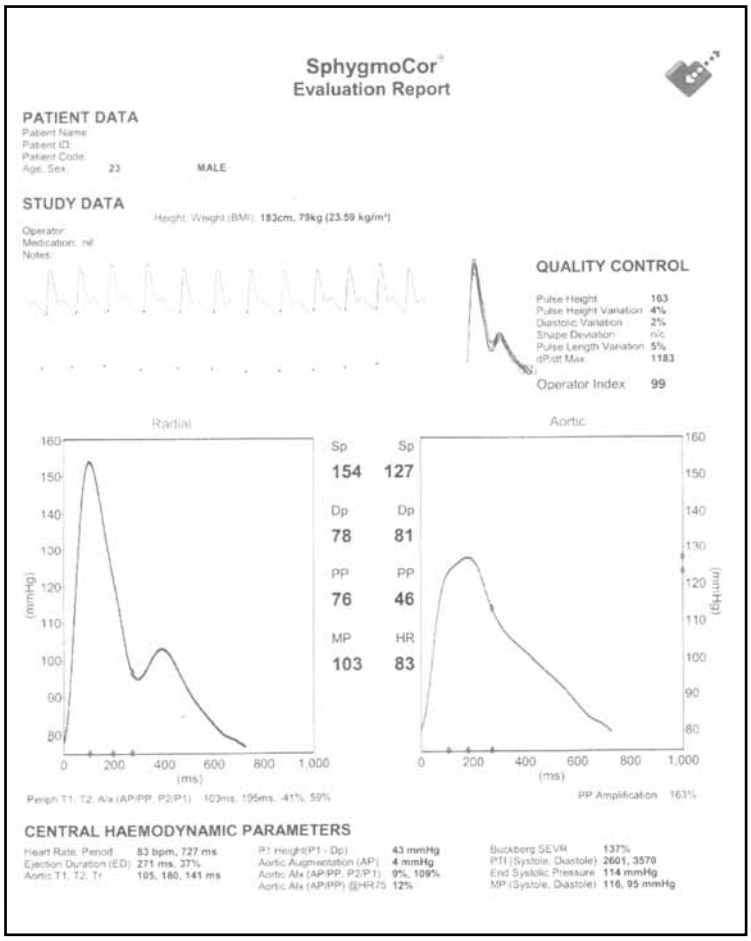

Figure 2. *SphygmoCor report showing a series of radial artery pressure waveforms above a series of central aortic pressure waveforms. Waveforms are ensemble-averaged into a single radial artery waveform (left) and a single central aortic waveform (right). The radial artery waveform is calibrated to brachial cuff SP and DP (154/78 mmHg). The central aortic ensemble-averaged waveform is derived from the generalised transfer function applied to the harmonic components of the calibrated radial pressure waveform. Central aortic SP is 127 mmHg, 27 mmHg less than the brachial SP, and within the normal range.*

transfer function, which had been developed at St Vincent's with Ray Kelly and others. This is now shown in figure 3, and with a linear relationship seen for males and females between age 5 and age 70 years. The solid red lines represent the increase in central SP between 5 and 70 years for females while the solid blue lines show the increase in central SP in males. The individual points from 3 to 16 are from members of our family (blue for boys and red for girls), while the crosses show the relationship between pressure and age of a pediatric cohort studied at Royal Prince Alfred Hospital in Sydney by Professor David Celermajer and colleagues (again blue for boys and red for girls). The plateau for cuff brachial pressure corresponds to the age range where there is greatest difference between cuff brachial and aortic SP.

We contend that the brachial SP readings are incorrect. They are distorted. A diagnosis of hypertension is not warranted.

We have gained more information on this issue by recording pressure waveforms in the radial artery of children from age 2 to 18 years (figure 3). We have used the same transfer function method as used in adults, or a different method based on a technique used in the Omron pulse analysis device. Both give essentially the same results.

This investigation on spurious systolic pressure in youth requires further confirmation beyond what we can provide, and a number of studies do so. The approach does give comfort to frightened parents whose child has been diagnosed as having hypertension and could be rejected from a preferred career. It is being considered by life insurance companies whose acceptance of a policy may now be passed, or yearly payments may be adjusted. It is under consideration by medical officers in recruiting pilots and potential astronauts, including the Chinese airforce.

The method for generation of central pressure is now considered by global authorities writing guidelines for assessment of blood pressure. The test required involves recording the pulse on the radial artery by an electronic finger – by applanation tonometry. This requires an element of skill but takes less time than conventional cuff sphygmomanometry.

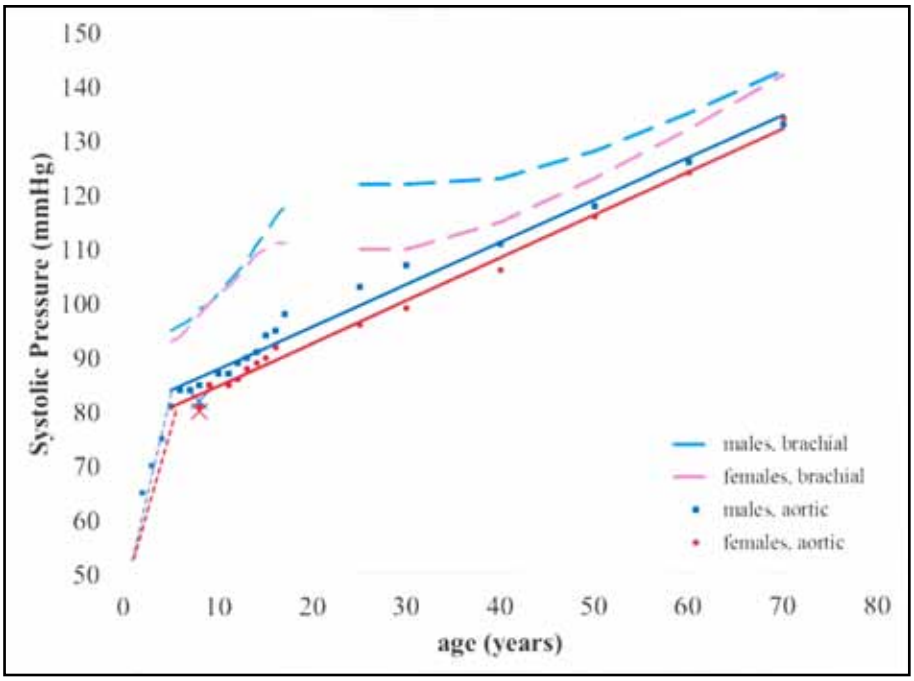

Figure 3. *Changes in male and female SP between and 2 and age 70 as in figure 1, together with derived central aortic SP from the radial artery waveforms of males (blue dots) and females (red dots). Data are consistent with a linear increase in aortic SP between age 5 and 70 years.*

Summary

"Spurious Systolic Hypertension of Youth" is a condition where a young person is considered to have hypertension on the basis of elevated (≥ 140 mmHg) brachial cuff systolic pressure, but diastolic and mean cuff pressures are normal. Subjects are usually tall, athletic, fit young males. Their radial artery pressure waveform shows a narrow systolic peak which is not seen in the central (carotid or aortic) pressure wave; their central aortic, SP is normal, and this can be demonstrated by generation of the central aortic pressure wave from the radial artery pulse wave measured non-invasively by applanation tonometry. This is a phenomenon of normal growth and development that we have confirmed by prospective studies of children and young adults from 3 to 20 years of age. This condition is now recognised as innocent in European and Asian guidelines on hypertension but not yet in US or Australian guidelines.

Prof Phillip Stricker
Dr Alex Blazevski

Focal Therapy for Prostate Cancer

Prof Phillip Stricker

Dr Alex Blazevski

Prostate Cancer (PCa) is among the leading causes of cancer-related death in men.[1] The treatments currently available for localised PCa include radical prostatectomy (RP), radiotherapy (brachytherapy or external beam radiotherapy) or active surveillance. Radical treatment is associated with significant side effects that can have a detrimental impact on the quality of life of PCa patients.[2,3] This had led to increased interest in improving current techniques and developing new PCa treatments.

In focal therapy only the tumour is targeted, while sparing adjacent anatomical structures that are of importance for urinary, bowel and sexual function. At present, focal therapy is being evaluated in patients with intermediate-risk PCa, a population in which the equilibrium of quality of life versus the oncological benefit of treatments is delicate.[4] In this group of patients, whole-gland therapy is considered overtreatment with minimal benefit and it is here that focal therapy may have a role.

A significant proportion of men are at risk of developing PCa in their life due to longer life expectancy. In 2017 there were 16,665 new PCa diagnoses in Australia and approximately 3000 deaths.[6] This reflects the main challenge we face in PCa care. While a lot of men are diagnosed in their life with PCa a significant part of these men will not die of the disease. We are currently not able to accurately differentiate those patients that require treatment from those that should not be treated.

Biology of Prostate Cancer

Focal therapy aims to treat patients with localised intermediate-risk PCa. In this group PCa is usually slow growing, with a long preclinical phase before progressing to clinically significant disease (if at all). The ProTect, the SPCG-4 and PIVOT trials have showed us that the majority of patients with low-risk disease do not need to be treated and that for intermediate-risk PCa there is a long window of opportunity to treat before clinical progression or PCa-specific mortality occurs.[7,8]

The aim of focal therapy is to ablate the index lesion. This is based on the theory that metastatic disease or death is due to the potential monoclonal origin of metastatic PCa.[9,10] In a recent study, men with metastatic PCa were invited to donate their bodies in the event of death. Thirty patients with 94 metastatic lesions were analysed using high-resolution genome-wide single nucleotide polymorphism and copy numbering. It was found that the origin of separate metastatic lesions in these men derived from the same single

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genomically aberrant PCa cell.[9] This has opened the door for focal lesion-based treatment, with the rational that high-volume lesions may be the cause for metastatic disease derived from a monoclonal origin, while smaller 'satellite' lesions would not exhibit metastatic potential.

By treating the localised 'index lesion' (high volume and high-grade lesion) the risk for developing clinically significant PCa may be reduced.[10] Nevertheless, histopathological analysis of 100 RP specimens has shown that the disease is multifocal in up to 78% of patients. However, when all lesions were analysed it was shown that, apart from the index lesion, 99.4% of the remaining lesions were Gleason 6 or less and 87% had a volume less than 0.5 mL.[11] Critics of focal therapy argue that the multifocality of PCa jeopardises the effectiveness of a targeted approach. Long term oncological data following focal treatment of the index lesion will establish or nullify the theory behind this paradigm.

Introduction to Focal Therapy

The first experience with focal therapy for localised prostate cancer was published in 2008 by Onik et al. These authors ablated prostate cancer lesions using cryotherapy that were identified with transperineal-template mapping biopsies..[5] They were the first to show the feasibility and safety of this approach. Since then the concept of focal therapy evolved into several ablative approaches and patient selection and lesion identification has improved. Depending on the lesion location and size, the ablative field can range from whole-gland, to hemi-gland, hockey-stick or focal ablation **(Figure 1)**.

In general, the smaller the ablative field is, the more likely it is that minimal treatment-related morbidity occurs.[4] Different techniques have been evaluated for the ablation of prostate cancer lesions, the most frequently used are cryotherapy, high-intensity focused ultrasound (HIFU), irreversible electroporation (IRE), laser therapy, vascular targeted photodynamic therapy (TOOKAD) or focal radiotherapy e.g. Cyberknife.

	Low-Risk	Intermediate-Risk	High-Risk
Gleason Score	GS 6	GS7	GS >7
PSA	PSA ≤ 10 ng/mL	PSA 10-20 ng/mL	PSA ≥ 20 ng/mL
TNM	cT1-T2a	cT2b-2c	>cT3a

Table 1 - *Defined D'Amico Risk Groups in Prostate Cancer*

Why Focal Therapy is Needed?

As illustrated by the ProTect, the SPCH-4 and PIVOT trials, the benefit of radical treatment in patients with intermediate-risk prostate cancer is minimal, whilst exposing patients to significant morbidity. In focal therapy the aim is to improve the balance of oncological control versus functional preservation e.g. urinary continence or erectile dysfunction. In a recent systematic review by Valerio et al., the functional outcomes after focal therapy, the pad-free/leak free continence and potency rates following treatment ranged between 83.3-100% and 81.5-100% respectively.[12] Despite this promising side of functional preservation with focal therapy, none of the ablative techniques are in the current prostate cancer treatment guidelines since this new treatment concept lacks long-term (comparative) oncological data **(Figure 2)**.[4,13,14]

While this form of therapy is still investigational, it has been widely adopted worldwide as part of the comprehensive, patient tailored management plan for PCa. Focal therapy may be positioned between active surveillance and radical therapy in the treatment spectrum. Patients with localised lesions treated with focal therapy may then be re-stratified into an active surveillance protocol or if disease progresses may then require radical treatment, much like breast cancer and the progression from lumpectomy to radical mastectomy.

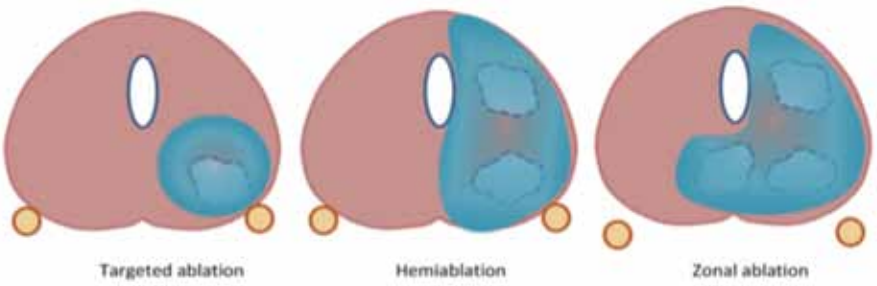

Figure 1 - *Focal therapy scenarios (red/yellow - neurovascular bundle; while - urethra; blue - ablation zone)*

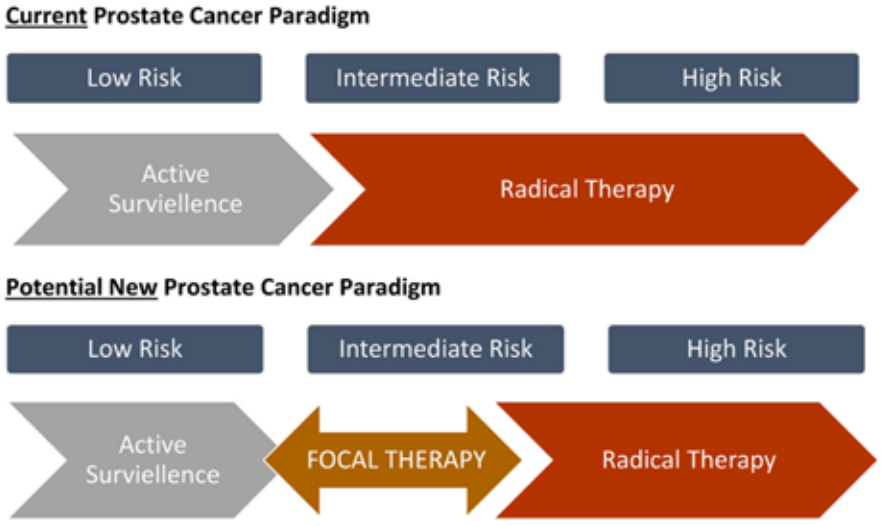

Figure 2 - Potential new treatment paradigm for prostate cancer

What do the Urological Guidelines say about Focal Therapy?

All the current prostate cancer guidelines including the EAU, AUA, NICE and NCCN guidelines do not recommend focal therapy as a current standard of care. Although the guidelines acknowledge that focal therapy may be the step forward for selected patients to minimise morbidity, they state there is a lack of long-term comparative oncological outcome data which compromises the uptake of the focal therapy concept in the major guidelines. The EAU, AUA and NICE guidelines all suggests that focal therapy only be offered to low- to intermediate-risk patients in the clinical trial setting.

Focal Therapy Consensus Guidelines

In consensus meetings led by Tay et al., Scheltema et al, and Muller et al., the following criteria were defined on the patient characteristics, selection methods and follow-up schemes.[21-23] Focal therapy can be performed in patients with:

- D'Amico low- to intermediate-risk prostate cancer, up to Gleason 4 + 3 = 7 (ISUP 3)
- Lesions may be up to 3 mL or 25% of the prostate gland if it is localized in one hemi-gland
- Acceptable to treat the index lesion (highest volume/grade) while leaving lesions containing low-volume Gleason 3+3 =6 in the contralateral lobe
- Recommended to select patients with multiparametric MRI (including targeted fusion biopsies) and systematic prostate biopsy
- Can treat patient based on template biopsy with negative MRI (however it is recommended that there is MRI co-registration as it exact lesion location and geometry is of paramount importance for treatment planning).

Following focal therapy, standardised follow-up biopsies should be performed to establish the oncological outcomes. Since prostate tissue is left untreated, there is a chance for retreatment on either a newly identified lesion in the contralateral lobe or an infield recurrence. The consensus meeting stated that a retreatment rate of <20% is acceptable.

Localising the Lesion

A combination of multi-parametric MRI (mpMRI) and transperineal template-guided mapping biopsy (TTMB) with image targeting are used to identify and locate the localised lesion. TTMB is superior to transrectal ultrasound (TRUS) guided biopsy as it is 95% sensitive to predict lesions >0.2 mL.[15] Standard TRUS biopsy is not suitable as it has been shown to under-grade and under-stage patients with PCa.[16] TTMB have shown to detect PCa in 51.6% of men that had (multiple) previous negative transrectal biopsies and 53.6% of these men had Gleason ≥ 7 PCa on TTMB.[17]

At present the main whole-gland imaging modality in PCa care is multi-parametric MRI (mpMRI). This includes T1- and T2-weighted imaging combined with dynamic contrast-enhancement (DCE) and diffusion-weighted imaging (DWI). Due to increasing use, research and technological advancements the ability to detect and rule out PCa with mpMRI has improved.[18] It is recommended that mpMRI be combined with systemic prostate biopsy for patient selection.[4] Tran et al., showed that the combination of TTMB with mpMRI is able to accurately detect locations within the prostate containing significant (Intermediate-risk) PCa.[19] The combination of mpMRI and TTMB was able to detect lobes containing significant PCa with a sensitivity of 97%, whilst being able to rule out existing PCa in the contralateral lobe in 91%.[19] This highlights that it is feasible to identify the majority of significant PCa lesions, but as lesions are still missed, further improvement in PCa diagnosis and localisation is of utmost importance to advance the field of focal therapy.[19]

A recent development in prostate imaging is (68-gallium) prostate-specific membrane antigen (PSMA) Positron Emission Tomography – Computerised Tomography (PET CT) scanning20. This has proven to be very specific in detecting high-risk intraprostatic tumours and metastatic disease, but the detection of low-to-intermediate risk intraprostatic tumours is still being evaluated.[20]

Irreversible Electroporation

Irreversible electroporation (IRE) is the modality of focal therapy performed in our institution. We are currently evaluating this treatment and offering it to patients after informed consent. IRE is a new technique based on a process known as electroporation, induced by generating micro-to milliseconds-long, high voltage electrical pulses between two or more electrodes. The pulsating current affects membrane repolarisation and creates 'nanopores' i.e. nanoscale disruptions of the cell membrane allowing molecules to pass into targeted cells.[24] The electroporation process can be temporary (reversible electroporation) or become definite (irreversible electroporation) depending on pulse frequency and duration, the intensity of the electric field and type of targeted tissue.[25] IRE is available as an ablative therapy modality in the form of the NanoknifeTM system (Angiodynamics Inc. Queensbury, New York).

Based on the principle of electroporation, IRE holds the potential to preserve connective tissue structures and limit damage to adjacent and vital structures e.g. neurovascular bundle, blood vessels.[26,27] It could be reasoned that ablative modalities such as high-intensity focused ultrasound (HIFU) or cryoablation, which solely depend on their non-selective destructive thermal effect, have a more detrimental effect on the surrounding tissue.

Furthermore, thermal ablative modalities have the limitation of heat sink i.e. loss of thermal intensity and ablative effect, when applied in proximity to major blood vessels, urethra and bile ducts. This 'heat sink' is defined as the difficulty to control the extension and therapeutic effectiveness of the ablation zone due to the effect of the blood circulation on local temperature development. Consequently, post-ablation histopathology analysis in thermal ablative modalities showed a transition zone between ablated vs non-ablated tissue due to partially damaged tissue by insufficient temperatures. The

targeted tissue within the electrical field of IRE showed a distinctive sharp demarcation from unaffected prostatic tissue, enabling more precise procedure planning **(Figure 2)**.[24-26]

The IRE console comprises two important components, monopolar needle electrodes (maximum of 6) and a low-energy direct current generator controlled by computer-based therapy planning **(Figure 3)**.

The Nanoknife™ system and needle electrodes are approved by the FDA for soft tissue ablation. IRE is performed under general anaesthesia because deep muscle relaxation (using rocuronium) is necessary to avoid severe uncontrolled muscle contractions. A brachytherapy grid and transrectal ultrasound is used to position and guide the IRE needles in a similar fashion as with the preoperative transperineal biopsy procedure. Guided by ultrasound imaging, 4 to 6 parallel electrodes are placed in the predefined target area (based on mpMRI and biopsy results). After the electrodes are in place, IRE parameters are entered into the planning software of the Nanoknife™ system and the ablation is performed **(Figures 4 and 5)**.

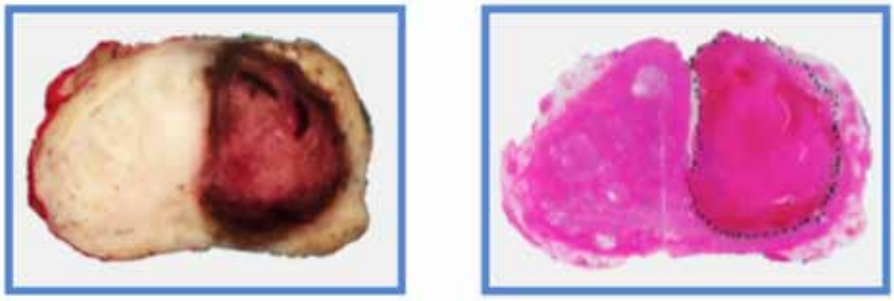

Figure 3 - *Histopathological evaluation showing sharply demarcated ablation zone on whole-mount pathology of radical prostatectomy specimen following IRE.*

Figure 4 - *IRE needle electrodes and the console*

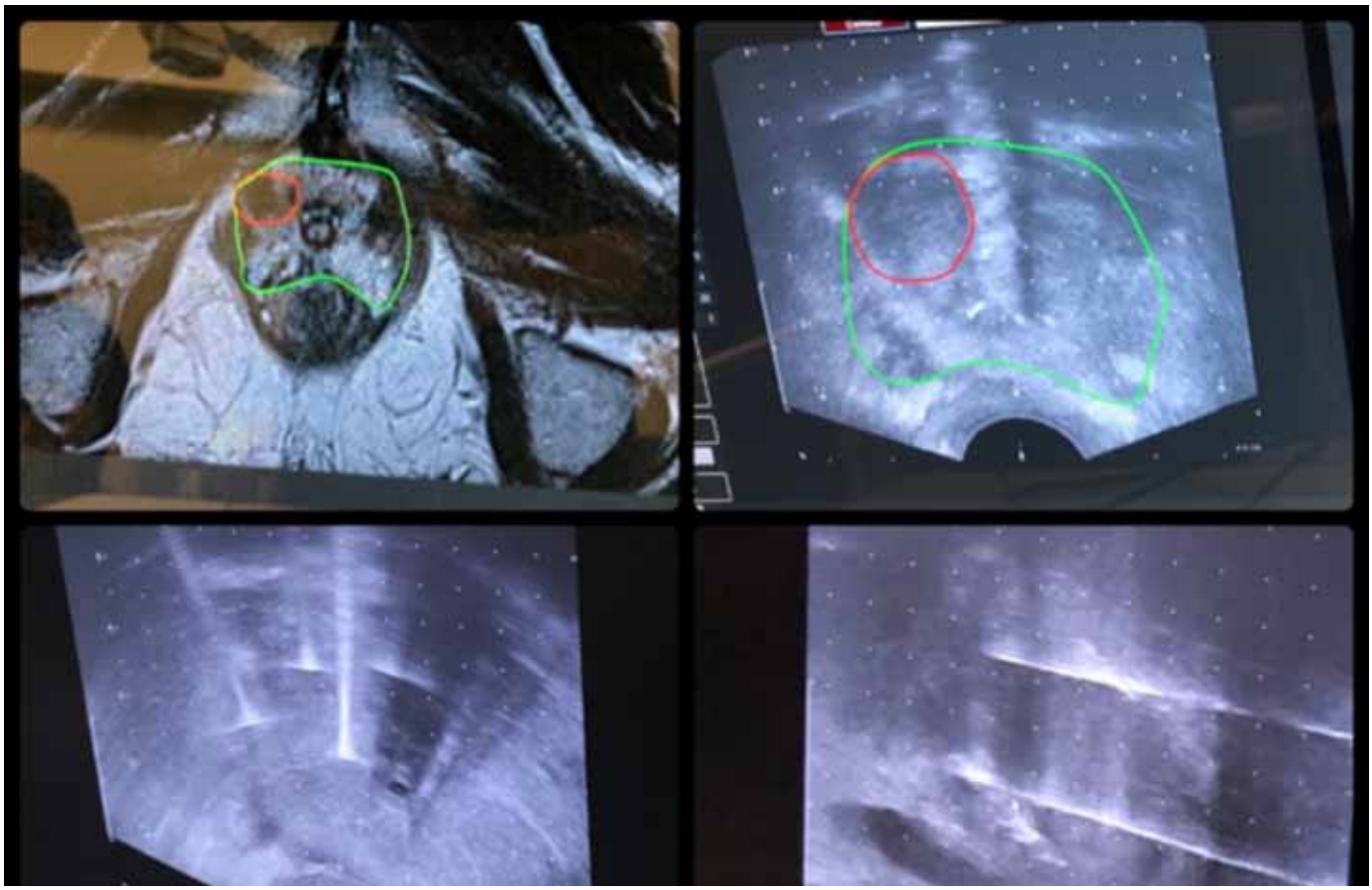

Figure 5 – *An example of how the lesion is targeted in Nanoknife procedure. Here the right apex lesion is identified initially on mpMRI (A). The lesion is contoured prior to surgery and then this image is fused with US during the procedure (B). In this case 4 electrodes are placed to encompass the lesion (C); we used up to 6 electrodes if required. A sagittal view is also provided (D).*

Results of Irreversible Electroporation at St Vincent's Prostate Cancer Centre

Nanoknife has been performed at St. Vincent's Prostate Cancer Centre since 2013. Over 200 patients with localised clinically significant prostate cancer have been treated with the procedure (primary and salvage).

Of the primary patients, 131 have had 12 months follow up (100 patients had a repeat biopsy at 12 months) –

- 90% (90/100) had in-field oncological control at 12 months
- 77% (77/100) were free of clinically significant prostate cancer at 12 months

After the initial learning curve and increasing the ablative margin from 5 mm to 10 mm –

- 97.3% (70/72) had in-field oncological control at 12 months
- 84.7% (61/72) were free of clinically significant prostate cancer
- 12.5% (9/72) had out-field failure

The quality of life (QoL) outcomes for the Nanoknife procedure has also been encouraging. While there is a decrease in urinary QoL at 6 weeks post IRE, this returns to baseline by three months **(Table 2)**. There is a 10-15% decrease in sexual QoL which does not return to baseline, however this is improving as we become more experienced with the procedure. Bowel function, physical function and mental function QoL are unaffected by the procedure **(Table 3)**.

Conclusions

Radical, whole-gland treatment of localised prostate cancer is increasingly being recognised as overtreatment and unnecessary in some men. Focal therapy may reduce toxicity of whole-gland treatment while still retaining oncological control. Given this, there has been significant interest in the development of focal therapy for the treatment of prostate cancer. Improved diagnostic imaging (multiparametric MRI and PSMA-PET scan) and better biopsy techniques has allowed better accuracy in locating the clinically significant cancer within the prostate. Multiple modalities of focal therapy have been developed but before wide-spread clinical introduction, clear, predefined, clinically relevant objectives are needed. It is recognised that in the low-risk group active surveillance is the preferred option while in the high-risk group radical treatment is necessitated. It is in the intermediate-risk group that focal therapy may have a role. Currently as there is no long-term comparative data, focal therapy must be regarded as an investigational modality. Nevertheless, if long-term benefit is proved (both functional and oncological) then focal therapy would represent a significant advancement in PCa care.

	In-field Oncological Control	Whole Gland Free of Clinically Significant PCa	In-field and Adjacent Failure	Out-field Failure
All Primary Patients	90% (90/100)	77% (77/100)	10% (10/100)	13% (13/100)
After Initial Learning Curve	97.3% (70/72)	84.7% (61/72)	2.7% (2/72)	12.5% (9/72)

Table 2 - Oncological outcomes of primary Nanoknife for localised prostate cancer

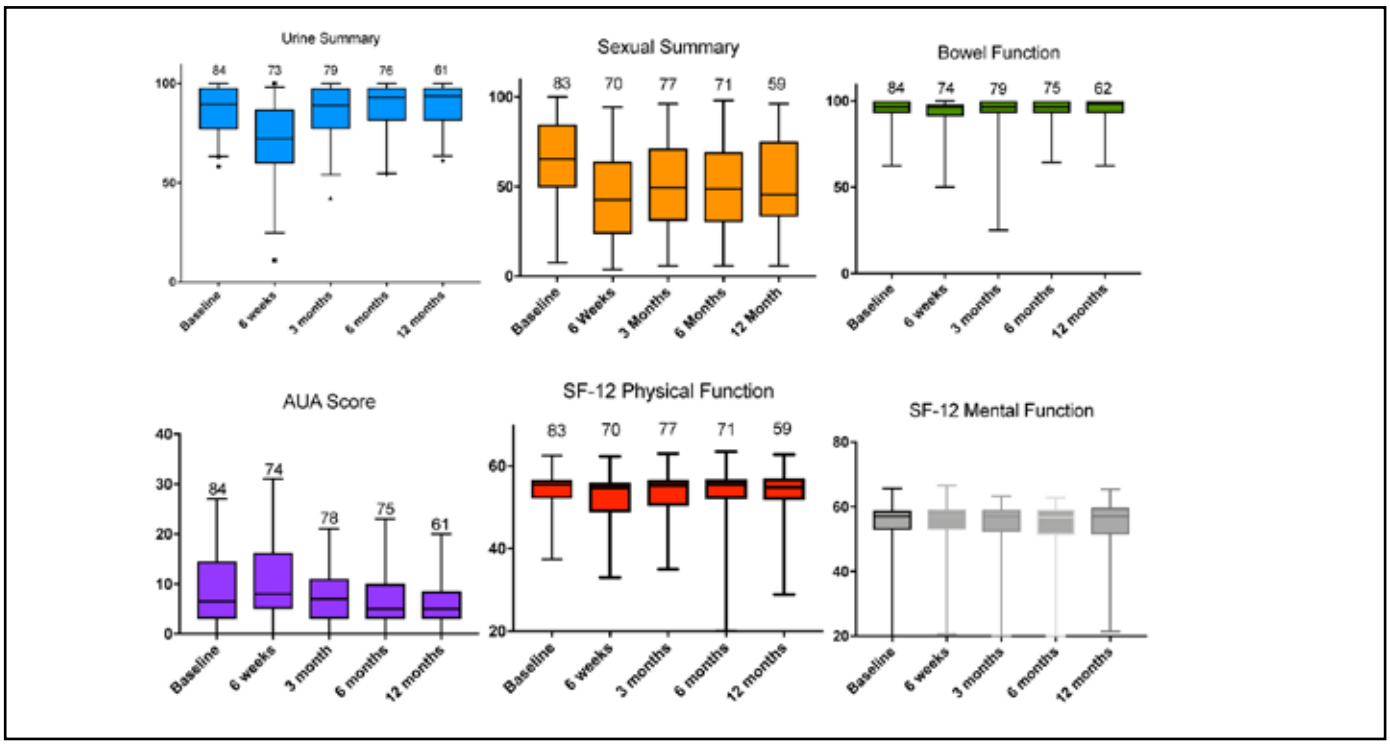

Table 3 - *Quality of Life (QoL) outcomes from primary Nanoknife*

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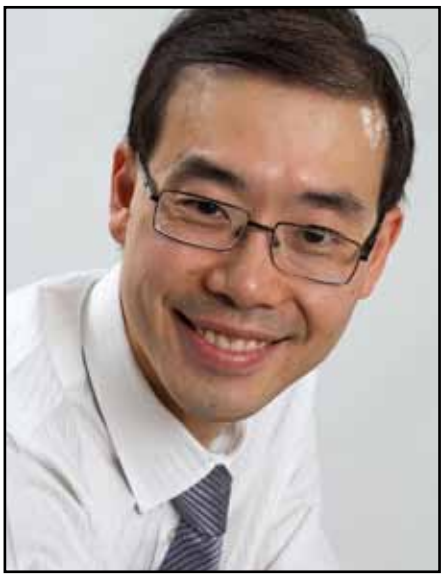
The role of inferior vena cava filters in venous thromboembolism: an update of best clinical practice



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Background

Anticoagulation is recommended for the management of venous thromboembolism (VTE) and aims to reduce the risk of incident and recurrent pulmonary embolism (PE). Some patients, however, have an active contraindication to anticoagulation **(Table 1)**. Additionally, other patients may develop recurrent PE despite being compliant on appropriate anticoagulant therapy, a situation labelled as 'anticoagulation treatment failure'. Inferior vena cava (IVC) filters have been often employed in these situations to mitigate the risk of recurrent PE and death.

IVC filters provide a means of mechanical thromboembolic prophylaxis and are designed to prevent the embolisation of large volume thrombus into the pulmonary arterial system. IVC filter insertion is performed in an interventional suite under fluoroscopy.

Although two types of IVC filters (1: permanent and 2: retrievable) have historically been used, retrievable IVC filters are now almost invariably used at St Vincent's Hospital. Permanent IVC filters are designed to remain in-situ for life, and do not have an easy mechanism to facilitate removal using an endovascular approach. Retrievable IVC filters are able to be removed using fluoroscopic techniques. Each manufacturer provides a guideline for the optimum time period during which removal should be attempted. Despite this, failure of retrieval is not uncommon, with retrieval success rates ranging from 78 to 100%.[1]

Indications for insertion

In clinical practice, IVC filters are often considered when VTE has been diagnosed and one of the following two situations complicating anticoagulant therapy are present:[2-4]

1. The presence of a strong contraindication to anticoagulant therapy **(Table 1)**.

2. Haemorrhagic complications have occurred while on anticoagulation, resulting in treatment cessation.

Table 2 lists other clinical situations where an IVC filter is often considered, but not routinely performed.[2-5] IVC filters are not indicated for patients who can receive oral anticoagulation, as they do not reduce the risk of symptomatic recurrent PE in these patients.[6] In addition, anticoagulation should be recommenced in patients who have VTE and an IVC filter in-situ once their risk of bleeding has resolved.[2, 3]

- Active, clinically significant bleeding
- Severe bleeding diathesis
- Severe thrombocytopenia or platelet function disorder
- Major trauma
- Imminent invasive procedure or obstetric delivery
- Intracranial or spinal tumour
- Severe, uncontrolled hypertension
- Clinically significant bleeding while on anticoagulation

Table 1: *Contraindications to anticoagulation*

- Massive PE in haemodynamically unstable patient as an adjunct to anticoagulation
- Mobile thrombus
- Acute VTE and poor cardiopulmonary reserve
- As mechanical thromboprophylaxis in major trauma patients unable to receive DVT prophylaxis and who are likely to have prolonged immobilisation

Table 2: *Other situations where IVC filter insertion is often considered, but not routinely performed*

Common outcomes associated with IVC filters

Recurrent DVT

Although filter placement may protect the pulmonary vascular bed, it does not reduce the risk, occurrence or extension of lower extremity deep vein thrombosis (DVT). In PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave), the largest existing randomised controlled trial involving IVC filters in patients with proximal DVT, IVC filters were associated with an increased incidence of recurrent DVT at 2 years (20.8% vs. 11.6%, P=0.02) and 8 years (35.7% vs. 27.5%, P=0.04).

IVC obstruction

This is one of the most feared complications of IVC filters. IVC thrombosis affects both permanent and retrievable filters, and may be caused by new thrombus forming at the site of the IVC filter, trapped embolus, or cephalad extension of an existing DVT. A very large case series found that IVC filter-related thrombus was found in 18.6% of patients, but only 2% had total iliocaval occlusion.[7] IVC thrombosis can result in IVC syndrome, which presents as bilateral lower limb and lower abdominal soft tissue anasarca. This leads to long term complications of chronic venous insufficiency and post-thrombotic syndrome. Endovenous techniques have been successfully used to recanalise IVC occlusion and reduce symptoms of venous insufficiency, but these are not without risks of bleeding as well as recurrent thrombosis.

Post-thrombotic syndrome

This is a complication that occurs not infrequently after DVT and can cause chronic lower limb pain, swelling, redness, and ulcers. Post-thrombotic syndrome is common in patients with extensive DVT who have an IVC filter in-situ, with published rates ranging from 5 to 70%.[8]

Breakthrough PE

This is an unexpected and uncommon occurrence following IVC filter insertion, with rates ranging from 3 to 7%.[8] This can occur if thrombi are sufficiently small enough to pass through the IVC filter or through venous collaterals around obstructed IVC filters. Embolisation can also occur if there is thrombus involving, or extending through, the IVC filter itself.

Device complications

Device-related complications include IVC penetration, filter fracture, filter embolisation and filter migration. These risks depend on the type of device. They are generally low, but rise with increasing dwell-time in the patient.

Procedural complications

IVC filter insertion is associated with a small (<3%) risk of peri-procedural complications such as device malposition, and procedural complications associated with internal jugular vein punctures (e.g. pneumothorax, haematoma, air embolism, inadvertent carotid artery puncture and arteriovenous fistula).[2] Complications are also possible during IVC filter retrieval. These include vascular perforation, significant bleeding, need for open surgery as well as retrieval failure. The risks have been quoted as ~4% if retrieval is attempted between 1 to 6 months after insertion, but may be higher if retrieval is attempted outside the timeframe recommended by the manufacturer.[9]

Best practice management following IVC filter insertion

Surveillance

Patients with IVC filters should be reassessed periodically between 3 to 12 months after placement, to reassess whether there is still need for the IVC filter.[2] The increased risk in device-related complications with increasing dwell-time is the reason for making sure that IVC filters are removed in a timely fashion when they are no longer needed. Consideration of the patient's life expectancy, cardiopulmonary status, and comorbidities can be useful in making the ultimate decision whether or not to refer a patient for IVC filter retrieval.

Recommencing anticoagulation in patients with a retained IVC filter if contraindications have resolved

Whether or not anticoagulation should be recommenced in patients with an IVC filter in-situ is determined

by whether the original indications and contraindications to anticoagulation are still present.[8] Anticoagulation should be resumed in patients with an IVC filter once contraindications to anticoagulation or active bleeding complications have resolved.[2,3] Anticoagulation reduces rates of IVC thrombosis and recurrent PE for patients with retained IVC filters, but is associated with an increased risk of bleeding.[10]

Summary (see Box)

IVC filters are a potential treatment option for patients who are at high risk for PE and unable to be treated safely with anticoagulation. Patients considered for IVC filter insertion should receive information regarding the benefits as well as the risks of having an IVC filter long term. Follow up is essential so that the ongoing need for mechanical thromboembolic prophylaxis can regularly reviewed, and a decision made regarding the likely time-frame during which the IVC filter should be removed.

Take home messages

- IVC filters reduce the risk of PE, have little-to-no effect on mortality, and are associated with an increased risk of recurrent DVT.
- Although IVC filters may reduce the risk of PE, they do not change thrombotic predisposition, nor do they decrease the incidence of lower extremity DVT.
- A retained IVC filter is associated with device-related complications, the incidence of which increases over time.
- Patients considered for a retrievable IVC filter should be informed about the benefits as well as the risks, which include the chance that the filter is unable to be retrieved, as well as the device-related complications.
- In most patients where the risk of PE was originally transient, the risks of leaving the IVC filter in-situ outweigh the complications risks associated with retrieval.
- A discussion with the patient regarding the timing of IVC filter removal should be held with the patient at a planned date during the patient's follow up.

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A/Prof Michael Neil

Use of Patient Matched Implants for managing large acetabular bony defects in revision Total Hip Replacement surgery

Dr Amir Kalanie

A//Prof Michael Neil

Introduction:

In Australia, a high-income country with the 7th highest incidence of total knee arthroplasty (TKA) and 15th highest incidence of total hip arthroplasty (THA) of the Organisation for Economic Cooperation and Development (OECD) countries, the volume of TKAs and THAs has increased by 198% between 1994 and 2014. According to one recent paper, this trend is likely to continue due to an aging population that is living longer and leading more active lives. Based on conservative estimates of population growth, it is predicted that there will be an increase of 219% in the number of total hip replacements (THRs) and 142% in total knee replacements performed annually by 2046.

Although the overall rates of revision of primary THRs has been on a decline since 2010 (down to 10% per annum), as the total number of THRs increase with time, so will the number of hips that will need to be revised.

The commonest cause for revision THR is loosening of the components due to normal wear and tear. The type of joint surfaces that are most frequently used in first time joint replacement in Australia are either a metal or ceramic ball on the femoral side forming a joint with a highly specialised plastic liner in the pelvis. After prolonged periods of friction and use (often ≥ 20 years), microscopic fragments of the plastic liner break away and get in behind the titanium cup in the pelvis. Our body treats these microscopic wear particles as foreign and mounts an immune response against them. This immune response in turn damages the bone, eventually leading to bone loss, cavity formation and loosening of the titanium acetabular component. At times these bony defects can become massive, creating an unstable, unsupportive pelvis **(Figure 1)** which in turn can make revision/re-do surgery a very challenging prospect.

For revision surgery to be successful, solid contact between the acetabular cup and the patient/host bone is required to allow for immediate stable long-lasting

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fixation to be achieved. In settings of significant bone loss however, initial stability can't be achieved with standard implants and therefore more complex techniques and prostheses have to be used to compensate for the lack of host bone and to achieve solid fixation of the implants.

Many different techniques have been described over the past few decades for tackling this difficult problem, all with varying degrees of success and each with its own specific shortcomings.

Due to the variability of the position, shape, size and severity of the bone loss and its relationship to the complex 3D anatomy of the pelvis, till recently, there's has been no one technique that has allowed the surgeon to adequately deal with any given scenario. The variety of treatment options available attests to the complexity of this problem. But all these treatment options aim towards a common goal that is healing of the unstable/unsupportive pelvis and achieving stable acetabular fixation.

Some of the techniques described in the literature include: placing the acetabular cup in high hip centre; using large hemispherical acetabular component, cup cage constructs; porous-coated jumbo acetabular components with porous metal augments; and allograft-prosthetic composites. Although these options substantially improve the orthopaedic surgeon's ability to reconstruct severe acetabular bone defects, they are complex, technically difficult and can be associated with high failure rates, necessitating further revision surgery.

Patient matched implants:

More recently with advances in imaging, bio-engineering and computing, it has become possible to accurately map out each patient's specific pattern of bone defect/pelvic instability and manufacture a custom implant that matches the exact defect for each patient. These custom implants are referred to as Patient Matched Implants (PMIs).

The process starts by obtaining a fine slice CT scan of the patient's pelvis. This is then converted into a very accurate 3D computer model of the patient's bony anatomy **(Figure 2)**. This image is then fed into specialised computer software that is then used to sculpt and shape a prosthesis that matches the patient's deformed bony pelvic architecture **(Figure 3)**.

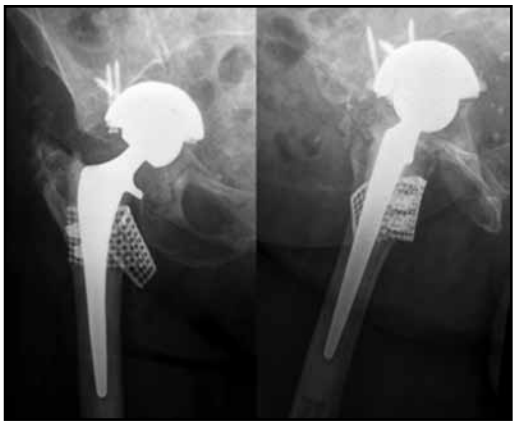


Figure1: *Large acetabular bony defect with superior and medial migration of the acetabular cup. There has been a complete failure of the supportive bony anatomy of the pelvis*

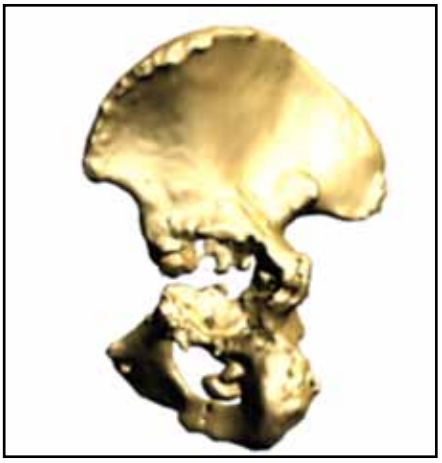


Figure 2: *3D CT reconstruction of a large pelvic bony defect used in planning a PMI*

Once the computer model is completed, with both engineers and the clinician happy that it accurately fits the patient's anatomy, a plastic 3D model of the patient's pelvis and the prosthesis are created **(Figure 4)**. This allows the surgeon to spend time studying the complex pelvic defect and gain a much valuable tactile and visual understanding of how exactly the implant will fit the pelvis days to weeks prior to the actual operation.

Once the surgeon is happy with the position and fixation of the PMI on the model provided, it is sent off for definitive manufacturing into it's final titanium alloy form. On the day of surgery, the plastic model of the pelvis and the PMI are both sterilized and made available to the surgical team, providing them with a valuable tactile and visual guide to important anatomic landmarks, making surgical exposure, which would normally be a very difficult and slow process, a more streamlined and safer exercise.

This ability to customise the prosthesis to the patient's specific pattern of pelvic bony defect rather the other way around has many advantages over the more traditional methods. To start, having an implant that is made for the patient reduces the operative time, blood loss and therefore overall physiologic stress on the patient. These implants have shown great safety profile in hand of an experienced revision surgeon and have shown to perform as well if not better than more traditional techniques (Clinical Orthopaedics and Related Research® February 2012, Volume

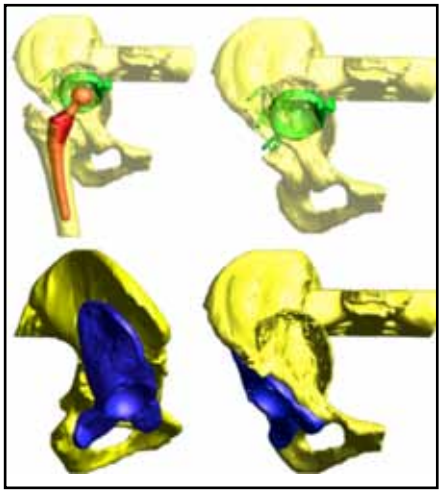


Figure3: digital models of the PMI using specialised computer software. This allows manufacturing of a prosthesis that allows maximum contact with remaining host bone

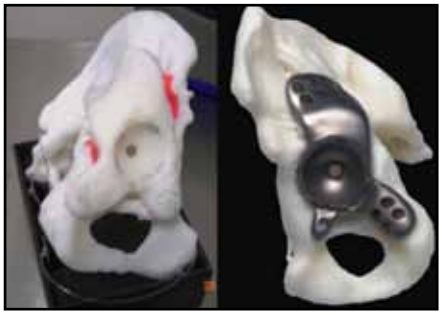


Figure 4: *Plastic model of the pelvis with a trial plastic implant seen in the left-hand image. Once the surgeon is happy with the final shape of the implant, the actual implant is manufactured (seen on the right)*

470, Issue 2, pp 428–434. A modified custom made triflanged acetabular reconstruction ring (MCTARR) for revision hip arthroplasty with severe acetabular defects, , Acta Orthop Belg. 2013 Feb;79(1):71-5.)

At St Vincent's Bone and Joint we recently reviewed our series of 12 PMIs with average follow up period of 50 months. This a relatively large series with one of the longest follow ups in the available literature. At the latest follow up, 11 of the 12 PMIs were radiologically well fixed, all patients had significant improvement in their functional scores and all pelvic discontinuities (instabilities) had healed.

Conclusion

Over the next two to three decades we will face a growing demand for revision surgery, with loosening and bone loss as the main causes. Some of these cases will present with large bony defects which will pose a significant challenge for both the surgeon and the patient. PMIs **(see Figures 5 & 6)** will become an important tool for orthopaedic joint surgeons over the coming years for dealing with complex and challenging pelvic bone loss in setting of total hip revision surgery. PMIs are a perfect example of how improvements in imaging technology, along with advances in computing and 3D printing are providing us with sophisticated tools needed to tackle these evolving Orthopaedic challenges safely and efficiently.

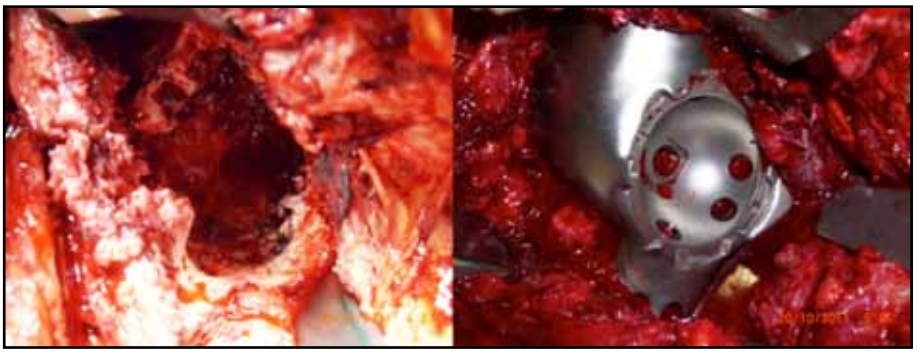


Figure 5: *Large bony pelvic defect seen on the left, with final Patient Matched Implant filling the defect on the right*

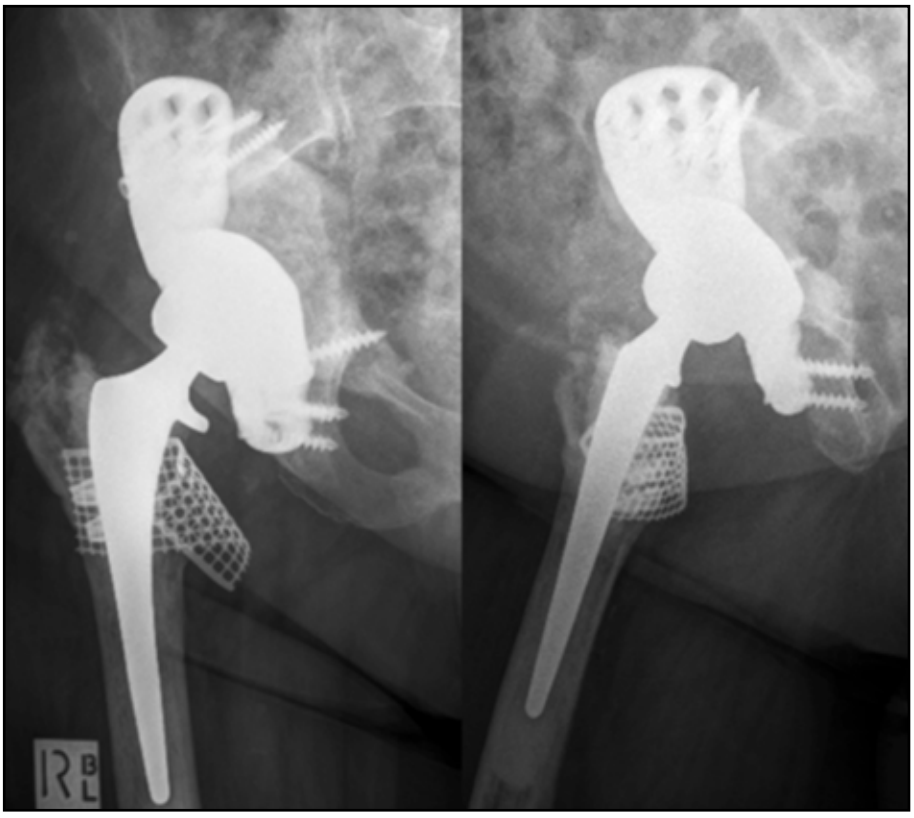


Figure 6: *Post operative x rays showing stable, well fixed implant with healing of pelvic discontinuity*

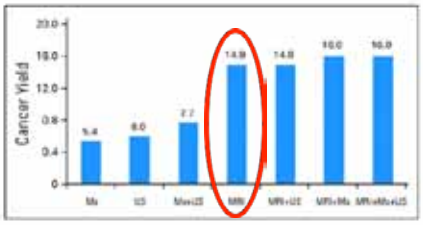
Lessons from Radiology

Medical Imaging, St Vincent's Private Hospital and St Vincent's Clinic

Case 1
Abbreviated Breast-MRI – A New Breast Screening Test

Dr Linda Borella
(MBBS, FRANZCR)

Breast cancer remains one of the leading causes of female deaths in Australia in women aged between 45 and 64.[1] Breast MRI is now widely recognised as the most sensitive imaging modality available for the detection of breast cancer. In contrast to standard breast imaging modalities such as mammogram and breast ultrasound, MRI utilises contrast enhancement as a biomarker to distinguish lesions with abnormal metabolic and vascular activity in the breast, including both intraductal and invasive cancers. It is now well established by research that MRI is more sensitive than mammography or ultrasound, or even both tests combined,

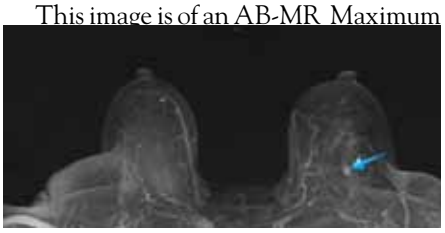


Furthermore, studies have shown that when MRI is used, there is no significant additional benefit to cancer yield by adding mammography (Mx), ultrasound (US) or both.[2]

Breast MRI is currently used for screening of women with high familial risk of breast cancer, staging or restaging of diagnosed breast cancer, solving problems that arise from conventional imaging and assessment of breast implants. Until recently, breast MRI has not been widely used for screening of breast cancer in average risk women due to availability, cost, time of the examination (typically around 25-30 minutes for a full scan) as well as misperceptions about the sensitivity and specificity of the test.

Abbreviated breast MRI (AB-MR) is starting to change all this. AB-MR is a "short" protocol breast MRI scan that utilises data from a limited set of pre-contrast and post-contrast scans for the detection of breast cancer.

This image is of an AB-MR Maximum



Intensity Projection subtraction image obtained 1 minute following IV contrast administration. The image shows a single 6 mm enhancing benign mass in the left breast.

AB-MR has been shown to be an effective tool for screening of patients at average risk of breast cancer. Research has shown that it is more sensitive than mammogram and/or ultrasound and is equally as effective as standard "long" protocol breast MRI for the detection of breast cancer. It takes less than 10 minutes to perform the scan and less than 30 seconds for an experienced radiologist to rule out breast cancer with a negative predictive value of greater than 99 per cent.[3] It can be used in women with breast implants, although does not assess the implants. It can also be used in patients with a history of breast surgery performed at least 12 months prior. AB-MR can be used for all breast tissue densities but is especially appealing as an effective screening test for women with dense breast tissue, a known risk factor for breast cancer.

It has been suggested that AB-MR might replace mammography for breast cancer screening in the future. It is currently used in an increasing number of centres across Europe and the United States. Recent updates to Practice Guidelines issued by the American College of Radiology recognises that as AB-MR has equal sensitivity and specificity to long protocols for breast MRI it may be a more cost effective screening tool.[4]

Australian guidelines for the use of AB-MR for breast cancer screening are yet to be established. Based on current scientific information patients can have an AB-MR scan every one or two years in addition to two yearly screening mammogram.

St Vincent's Clinic Medical Imaging & Nuclear Medicine is proud to be the first imaging practice in Sydney and one of the first sites in Australia to offer Abbreviated Breast MRI. Patient feedback thus far has been positive, with many commenting the test is easier and preferable to a mammogram.

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Case 2: Testuclar Adrenal Rest Tumours and Congenital Adrenal Hyperplasia

Dr William Lees
(MBBS, FRANZCR)

A 25 year old male with congenital adrenal hyperplasia (CAH) with 11-beta- hydroxylase deficiency, was referred for a scrotal ultrasound to exclude testicular adrenal rest tumours (TART).

The testes were both clinically normal and without pain, enlargement or mass lesion and thus the ultrasound was a screening referral and baseline evaluation.

Scrotal ultrasound depicted bilateral small adrenal rest tumours (stage 2). These are characterised by hypoechoic, round, well defined hypervascular intra-testicular lesions **(Figures 1 and 2)**.

TART's are usually multifocal and bilateral (75 per cent) and typically range in size from 2-28mm. They are uniformly benign and may respond to ACTH suppression by glucocorticoid therapy.

Staging is by Claahsen-van der Grinten: stage 1 : likely adrenal rests in the rete testis not discerned by U/S in neonate and paediatrics; stage 2 : become visible on U/S; stage 3 : further tumour growth compressing the rete testis in post pubertal CAH patients with oligo- or azoospermia; stage 4: further hyperplasia with fibrosis and focal lymphocytic infiltration; and stage 5: chronic obstruction with irreversible damage.

In summary, TART's in CAH are benign testicular lesions that can be safely monitored. TART's need not be confused with sinister testicular tumours based on imaging findings.

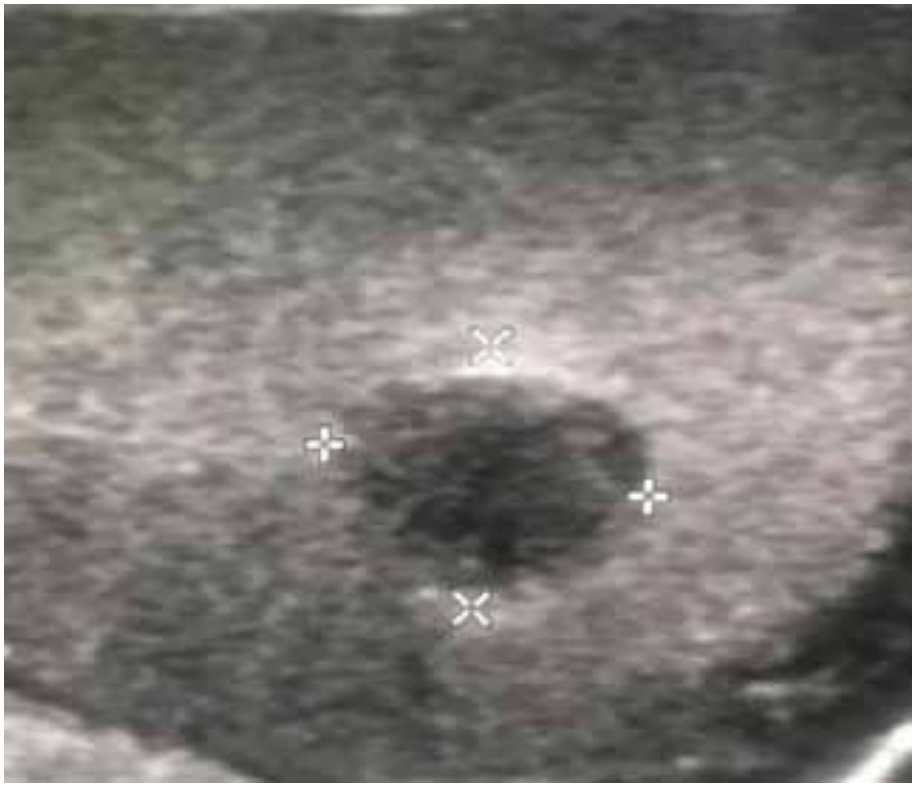


Figure 1: *Red arrow depicts a small testicular adrenal rest tumour.*

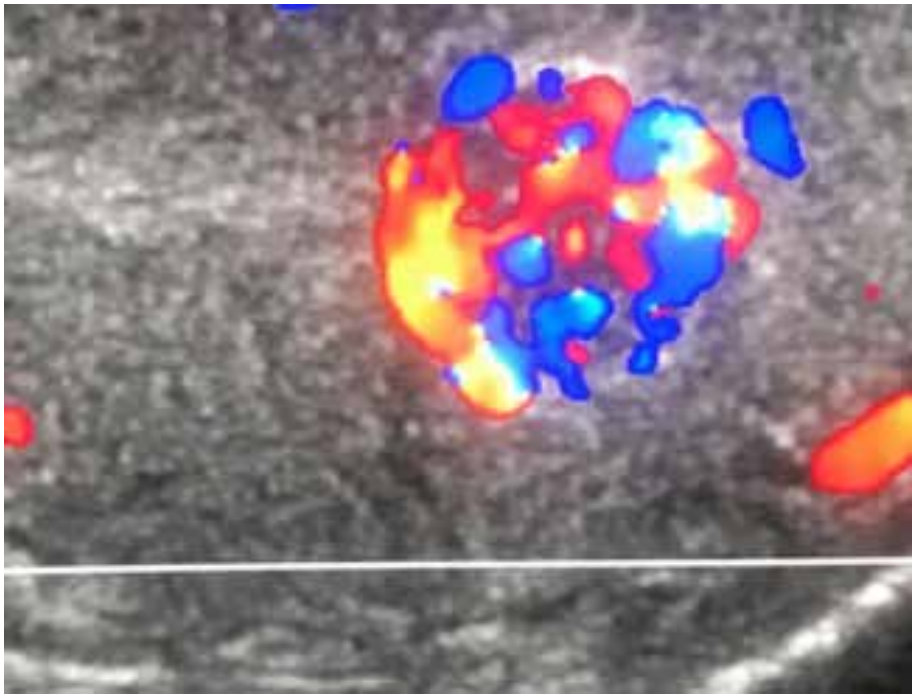


Figure 2: *Black arrow demonstrates tumour hypervascularity on colour Doppler flow imaging.*

Case 3: Radiation Myositis Presenting with Right Hip and Thigh Pain

By Dr Sebastian Fung (MBBS, FRANZCR)

A 51 year opd female presented with right sided poorly defined thigh, hip and knee pain for a number of weeks and difficulty weight bearing. She described a stiffness and swelling in her thigh and hip region.

There is a background history of metastatic breast carcinoma with known osseous metastatic lesions. The patient underwent MRI of the right hip and pelvis initially to ascertain the cause of the pain, as there was a clinical concern for further metastatic bony disease or pathological fracture.

The initial MRI **(Figure 1)** demonstrated the known osseous metastases in the femur, pelvis and acetabulum, but none of the lesions were sufficiently large or demonstrated cortical erosion to account for the patient's presentation. There was no cortical destruction associated to suggest impending pathological fracture and indeed no pathological fracture or marrow oedema was demonstrated.

However, extensive thigh muscle oedema was noted on the edge of the field of view on fat saturated T2 weighted imaging, prompting the need for further more dedicated imaging of this region. The provisional diagnosis at this stage was that of a pathological fracture and reactive soft tissue oedema.

On further enquiry, the patient reported that she had undergone radiotherapy to this region approximately six weeks prior, directly in the location of the muscle oedema. More dedicated imaging of this region **(Figures 2 and 3)** revealed a well demarcated rectangular region of muscle oedema circumferentially involving the thigh, affecting quadriceps, adductor and hamstring musculature, along with their fascia and the subcutaneous tissues. This occurred around a metastatic lesion in the femur which had been irradiated. Sub-fascial intermuscular fluid was also noted.

Figure 1 – *Coronal image of the hip showing multiple bony metastases (blue arrows) and marrow infiltrate as well as thigh muscle oedema (red arrows) extending beyond the field of view*

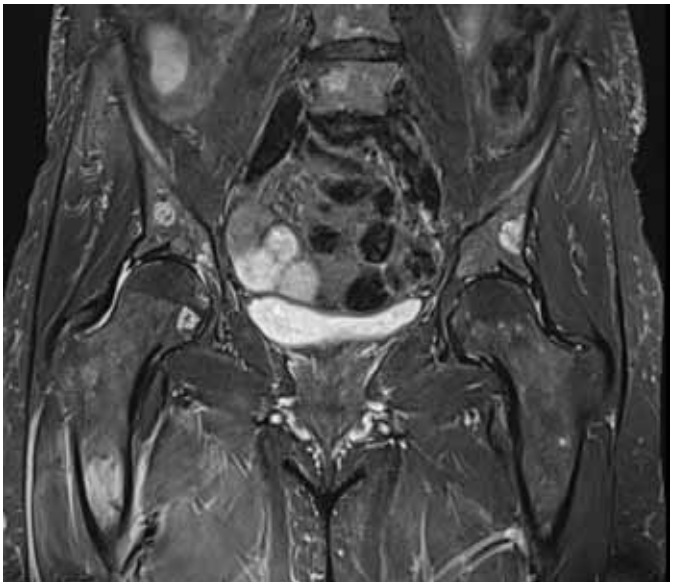


Figure 2 – *the patient was recalled for more dedicated imaging of the right thigh with coronal fat saturated imaging demonstrating a demarcated linear margin to the muscle oedema (blue arrows) surrounding a metastatic lesion in the femur (red arrows)*

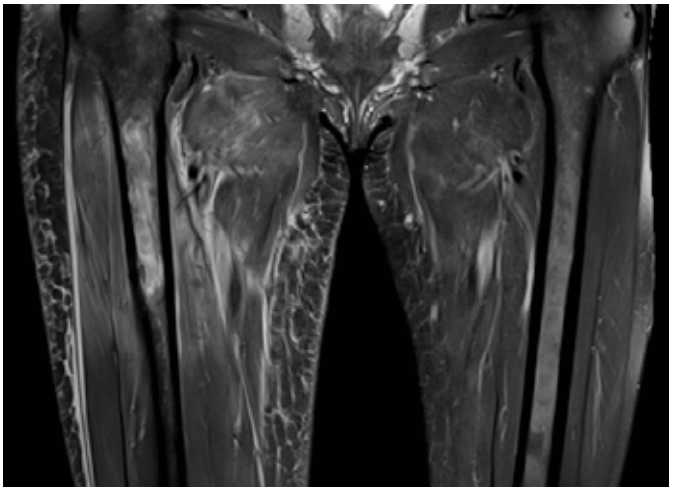
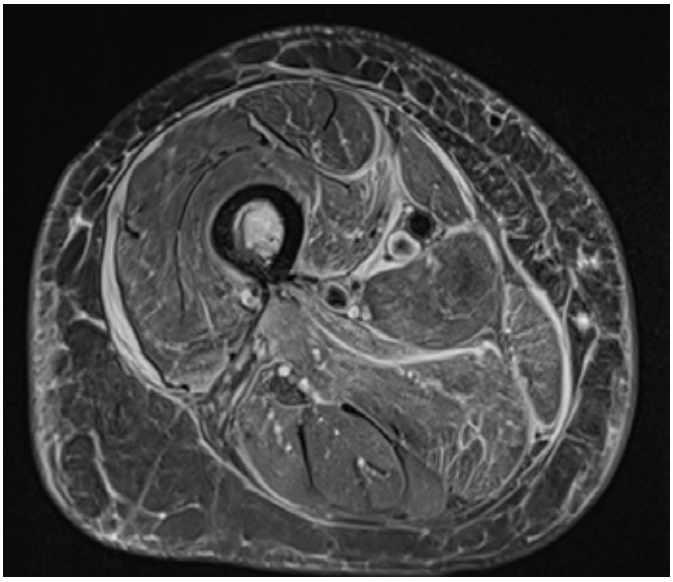


Figure 3 – *Axial T2FS sequence showing circumferential muscle oedema and peri-fascial fluid involving the adductors, hamstring and quadriceps as well as the subcutaneous tissues.*



The diagnosis was that of radiation myositis. This case demonstrates the importance of interpreting MRI images in combination with the relevant history. Imaging in this case was particularly instructive, given that the soft tissue changes were centred on the irradiated bony metastasis and the sharply defined linear margins of the changes were characteristic of a radiation field.

Occupational and Environmental Risk Factors Associated with Breast Cancer

Michael J. Jenson

Introduction

Breast cancer is a major burden to our society. This year (2018), The Australian Institute of Health trend shows there will be 18,300 new cases of breast cancer in Australia (145 in males), highlighting breast cancer as the most common malignancy in this country (males and females combined).[1]

Currently 13 per cent of all new malignancies are due to breast cancer with one in eight females, living to the age of 85, developing this disease. It is estimated that some 280,000 women with a diagnosis of breast cancer are living in Australia, some undergoing treatment, many in disease free long-term survival, while a number endure side effects of effective, modern therapy. With early diagnosis and effective treatment most patients can expect long term survival, currently 90 per cent at five-years and 82 per cent at 10 years.[2]

Less than five per cent of breast cancer presents in the under forty-year age group. The incidence rises rapidly, peaking around age 60-65, and remains high, with a small decline, through to the mid 80s.

Apart from being female and getting older, commonly acknowledged risk factors explain 40% of new cases. These include: inherited genetic mutations (5-7 per cent); lifestyle factors which increase risk (such as obesity, smoking and alcohol and hormonal influences, notably early menarche, the pill, late menopause and post menopause hormone replacement therapy); family history and race, with white females in the USA closely followed by Australia and New Zealand at highest risk. High socioeconomic status also increases risk.

Reducing the incidence of breast cancer has stimulated an interest in recognizing and minimizing possible environmental and occupational risk factors. Many epidemiological case control and cohort studies demonstrate an association between breast cancer and industrial risk.

Michael J Jensen FRACS, FACS, Surgical Oncologist, St Vincent's Clinic

Environmental and Occupational Factors

a. Ionizing Irradiation

Ionizing irradiation causes direct damage to normal cells and their DNA which leads to cellular proliferation and cancer.

Historically, survivors after the atom bomb explosions in Japan, developed an increased incidence of male and female breast cancer. This was particularly recorded in young women exposed prior to their first pregnancy, with a four- fold increase for women exposed under 20 years.[3,4]

Radiation Therapy, used in the treatment of childhood and young adult malignancy may increase new malignant risk, e.g. young patients with lymphoma, treated by mantle radiation therapy, are at increased risk of later developing breast and thyroid malignancy.

This radiation risk was recognized in the fifties for workers in the nuclear power industry, military service and medical diagnostics, prior to current preventative measures.[5]

The challenge of radio-protection is very real for today's Interventional Radiologists and Clinicians undertaking regular fluoroscopic examinations e.g., cardiac and vascular colleagues, placing stents.[6] The cancer risk from exposure to ionizing radiation is greater in staff with an underlying, often unknown, gene mutation which includes single nucleotide polymorphisms (SNPs).[7,8]

b. Night and Shift Work - light at night - melatonin

Michael J. Jenson

Melatonin acts by multiple pathways effecting the initiation, promotion and progression of breast cancer.[9,10] In vitro, melatonin suppresses growth of breast cancer stem cells (mammospheres) by binding to estrogen response sites on the OCT4 gene in human breast cancer stem cells.[11] Melatonin also acts as a selective estrogen receptor modulator (SERM) via decreased expression of alpha estrogen receptors. High melatonin decreases the motility and invasive capability of breast cancer cells in cell line culture studies.

The 24hour diurnal cycle of sleep and wakefulness is controlled by melatonin, "the hormone of darkness". During daylight, melatonin production from the pineal gland is turned off by exposure to sunlight. The principle element of daylight that reduces production of melatonin is blue light, the narrow band of the electromagnetic wave (visible

light) spectrum between 450 and 495 nm. Blue light disrupts melatonin by transmitting signals, via receptors in the retina, to the pineal gland. Normally as sunlight fades melatonin levels rise, with levels peaking at 1-2 am.[12,13]

Many artificial sources of blue light have the ability to reduce melatonin production at night. These include computers, smart phones, ipads and television. Blue light is a major component of night lighting, especially when night light is supplied from LED (light emission diode) and fluorescent sources. Incandescent light bulbs, producing yellow light, have a lesser impact on reducing melatonin levels.[14]

A higher incidence of breast cancer is recognized in occupational studies of shift and night workers including nursing staff, airline stewardesses, shift workers in the transport industry and night janitors. A meta–analysis, of observational studies over many years (18), updated in 2017, supports an increased risk of breast cancer with night shiftwork. This is apparent after 20 years of routine shiftwork. If many consecutive nights are routinely worked then a shorter risk period is recorded.[15,16]

A prospective cohort study reported nurses working night shifts of more than thirty shifts annually, doubled their risk in post -menopausal females after 15 years.[17,18]

In a Harvard study, of exposure to neighbourhood light at night (LAN), the homes of 109,672 nurses were geocoded and followed prospectively from 1999 to 2013. The average light level in the immediate neighbourhood at night was estimated from satellite images taken by the Defence Meteorological Satellite Program from outer space. The study found a direct relationship between the later risk of developing breast cancer and the community's exposure to brilliant night light. Breast cancer incidence was highest in females exposed to excess light and diagnosed prior to the menopause.[19,20] There was an additional association with smokers and night shift work.

A meta-analysis of six of seven international studies of flight crews showed a modest (44 per cent) elevated risk of breast cancer compared to the general population. Several studies from Sweden, Finland and Japan (23,995) examined cancer risk for stewardesses versus their hours of sleep. In Norwegian air hostesses and air crew from Iceland, the incidence of breast cancer was significantly elevated with repeated long haul flights over the north pole. [21,22]

Two possible mechanisms for flight crew should be considered: disruption of circadian rhythm (working at night, shiftwork, crossing time zones) ; and exposure to cosmic (a form of ionizing) radiation.[23] A 2017 report, analyzing four Scandinavian studies with increased risk of breast cancer in airline stewardesses, demonstrated levels of exposure to cosmic radiation varying with latitude, altitude and solar flares. Airline crews flying regular, long distance, high altitude routes, especially polar routes (near geomagnetic poles) are at particular risk.[24]

Genetic polymorphisms have also shown a strong association with breast cancer incidence in night and shift workers.[25]

c. Environmental/Industrial Risk factors

Excessive exposure to polycyclic aromatic hydrocarbons (PAHs), pesticides, organic solvents and heavy metals have been associated with breast cancer.

PAH's, a group of over 100 chemicals, are largely generated by the incomplete combustion of carbon containing fossil fuels –coal, crude oil, wood and gasoline as well as from cigarettes (passive smoking). PAHs produced from these sources include benzpyrene, dibenzanthracene, 1-nitro pyrene and monocyclic benzene, all established experimental breast carcinogens and linked to breast cancer in many environmental studies.[26]

Second hand cigarette smoke is well established as a toxic air contaminant and is believed more significant in its effect on breast cancer, than on lung cancer.[27] SHS contains over sixty carcinogens, the strongest carcinogen being the nitrosamine (NNK). Studies implicate NNK with breast cancer risk, significantly in younger women, with sensitive receptors in breast tissue with a thousand-fold greater affinity for NNK than for nicotine. The alpha9nAChR receptor present in breast tissue has been identified with NNK mediated cell proliferation and the molecular signaling cascade leading to breast cancer. [28]

Pesticides (insecticides fungicides and herbicides) acting as endocrine disruptors have long been implicated with breast cancer.[29] Two main groups are the organochlorines and the organophosphates. Organochlorines (DDT and polychlorinated biphenyls) are strongly carcinogenic and are now banned. A 2013 study in Chile of aerial spraying with the organophosphate malathion showed 5.7 times the incidence of breast cancer compared to matched populations in adjacent non-effected cities.[30] A local study, supported by University of Western Australia, examined spray drift from agricultural pesticide application areas and later elevated breast cancer incidence.[31]

Organic solvents, such as benzene and trichloroethylene are listed as human carcinogens by the International Agency for Research on Cancer and the US National Toxicology Program.[32] A significantly elevated incidence of estrogen receptor positive breast cancer is demonstrated with solvent exposure in specific occupations, especially clinical laboratory technologists and technicians. Danish and Canadian studies report that the risk of breast cancer, significantly applied to workers who were repeatedly exposed to solvents at a young age.[33] Solvent, at risk use, is also present in the laundry and dry cleaning industries, especially for women exposed prior to their first pregnancy.[34] Shoe factory workers in Italy, using benzene based glues, have developed increased rates of breast cancer.[35]

Heavy metals act as metallo-estrogens. Two classes, oxyanions and bivalent cations, are recognized as being carcinogenic. Oxyanions include arsenic, antimony and nitrites. Bivalent cations include cadmium, cobalt, copper, nickel, tin, lead and mercury.

Women employed as metal platers and coaters, who are particularly exposed to cadmium, are reported with a higher incidence / mortality from breast cancer, significantly among African American workers.[36]

Metals are common environmental contaminants from industrial sources in the power industry and transport, municipal waste sites and agricultural sources using agrochemicals.

They cause pollution of aquatic ecosystems and become incorporated into the food chain.[37]

d. Low and Mid Frequency Electro Magnetic Fields (EMFs)

Low to mid frequency EMFs, found in the non - ionizing part of the electromagnetic wave spectrum, do not cause direct damage to cells or to DNA. These ubiquitous magnetic fields are associated with power lines, electrical appliances, radio and TV waves, microwaves, as well as infra- red and visible light. EMFS are present in the home, at work, school and many public places.

Low frequency EMFs may increase the incidence of breast cancer by inhibition of the production of melatonin.[38] Scandinavian studies and a US case control study, report a modest, increased incidence of breast cancer from both occupational and residential exposure to high voltage power lines. Power lines produce the lowest frequency of electromagnetic waves.[39] One Norwegian study reported a 60% increased risk of estrogen receptor positive breast cancer, with the risk greatest in pre-menopausal women.

A scientific review of the world's largest breast cancer cluster in Toowong, Brisbane of young ABC newsreaders employed between six and sixteen years showed a 12 per cent increase in breast cancer risk per year of employment, argued as being explained by excessive exposure to EMF's combined with long hours of shift work and smoking.[40,41]

Despite the above evidence, the latest (2018) National Cancer Institute statement does not support an increased risk of breast cancer due to EMF's.[38]

Summary

The Western Australia Cancer Council has created a priority list of 38 known or potential carcinogenic risk factors in seven categories: combustion products, inorganic dusts, organic dusts, metals, radiation, other industrial chemicals and shiftwork (circadian disruption).

In vitro and epidemiological studies are voluminous but not absolute in establishing the pathway to breast cancer. As such, evidence is difficult to interpret so that international surveillance programmes recording occupational exposure to carcinogens are important.(42)

A common theme in this paper is recurrent exposure, particularly in the relatively immature breast before pregnancy, to a combination of offending carcinogenic agents and lifestyle events increasing future breast cancer incidence (at times enhanced by an underlying, even minor, genetic defect). It is apparent that multiple factors coincide in the cascade of events leading to breast cancer.

Raising awareness of occupational, industrial and environmental risk may become part of the solution to reducing the incidence of our nation's commonest malignancy.

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St Vincent's Clinic Foundation – 2018 Grant Recipients

- **St Vincent's Clinic Foundation 25 Year Anniversary Grant – $100,000**
  Prof Sally Dunwoodie – Victor Chang Cardiac Research Unit
  "Determining the extent to which NAD deficiency is the cause of miscarriage and congenital malformation"

- **SVPHS Ladies' Committee Sr Mary Bernice Research Grant – $100,000**
  Prof Jerry Greenfield – Garvan Institute of Medical Research
  "Personalised medicine in prediabetes - towards preventing diabetes in individuals at risk"

- **Adult Stem Cell Research Grant – $100,000**
  A/Prof John Moore – St Vincent's Health Network Sydney
  "Exploring the role and kinetics of T memory stem cells in haematopoietic stem cell transplantation for autoimmunity"

- **Tancred Research Grant – $50,000**
  Prof Anthony Kelleher – St Vincent's Health Network Sydney
  "Analysis of T follicular helper cell responses to influenza vaccine, by single cell RNA sequencing transcriptomics"

- **K&A Collins Cancer Grant – $50,000**
  Prof Diane Fatkin – Victor Chang Cardiac Research Unit
  "Are cardiac complications following doxorubicin chemotherapy more common in carriers of titin mutation? Insights from a zebrafish model"

- **Thelma Greig Cancer Grant – $50,000**
  A/Prof Anthony Joshua – Garvan Institute of Medical Research
  "DNA repair defects as a predictor of response to novel treatments in advanced castrate-refractory prostate cancer"

- **Froulop Research Grant – $30,000**
  Dr Nicola Smith – Victor Chang Cardiac Research Unit
  "Investigating the interplay between the sympathetic nervous system, anxiety and gender on blood pressure homeostasis"

- **Annual Grant 1 – $30,000**
  Prof Robert M Graham – Victor Chang Cardiac Research Unit
  "Elucidating the pathophysiology of spontaneous coronary artery dissection"

- **Annual Grant 2 – $30,000**
  Prof Samuel Breit – St Vincent's Health Network Sydney
  "The TGF-B superfamily cytokine Macrophage Inhibitory Cytokine-1 (MIC) protects from development of prostate cancer"

- **Annual Grant 3 – $30,000**
  Prof Neil D Watkins – Garvan Institute of Medical Research
  "The genomic basis of locoregional metastasis in head and neck squamous cell carcinoma"

- **Annual Grant 4 – $30,000**
  Dr David Herrmann – Garvan Institute of Medical Research
  "A novel biosensor to predict prostate cancer spread - implications for anti-invasive drug discovery"

- **Annual Grant 5 – $30,000**
  Dr Tim Molloy – St Vincent's Centre for Applied Medical Research
  "Using stem cell models to characterise cohesin mutations in acute megakaryoblastic leukaemia"

- **Annual Grant 6 – $30,000**
  A/Prof David Muller – St Vincent's Health Network Sydney
  "Combined cardiac magnetic resonance imaging and arterial tonometry to non-invasive quantitate ventricular pressure-volume relationships and vasculo-ventricular interaction"

- **Annual Grant 7 – $30,000**
  Prof Jamie Vandenberg – Victor Chang Cardiac Research Unit
  "Why are hERG K+ channels so promiscuous with respect to drug binding?"

- **Annual Grant 8 – $30,000**
  A/Prof Mark Danta – St Vincent's Health Network Sydney
  "Hepatic Encephalopathy DECMRI (HED-M) Study"

- **Multidisciplinary Patient Focused Research Grant 1 – $25,000**
  Mr Jeff Breeding – St Vincent's Health Network Sydney
  "A pilot single ceNtre study of the impActs and imPlications of the quality of sleep for adult ICU patients (NAP-ICU)"

- **Multidisciplinary Patient Focused Research Grant 2 – $25,000**
  Ms Claudia Woolf – St Vincent's Health Network Sydney
  "Club Connect: A healthy brain ageing cognitive training program for older adults"

- **Multidisciplinary Patient Focused Research Grant 3 – $25,000**
  Ms Elise Crothers – St Vincent's Health Network Sydney
  "Diaphragm ultrasound in lung transplant patients study (LUST)"

- **Multidisciplinary Patient Focused Research Grant 4 – $25,000**
  Ms Bonnie Lai – Garvan Institute of Medical Research
  "Dietary intervention to improve the gut microbiome and body composition for better physical health in newly diagnosed type 1 diabetes mellitus"

- **Multidisciplinary Patient Focused Research Grant 5 – 12,000**
  A/Prof Nigel Biggs & Ms Amanda Fullerton – St Vincent's Private Hospital Sydney
  "Utility of remote mapping of cochlear implants"

- **Multidisciplinary Patient Focused Research Grant 6 – 25,000**
  Ms Julie Gawthorne – St Vincent's Health Network Sydney
  "Can Emergency nurses safely and effectively insert ultrasound guided fascia iliaca blocks compared to medical practitioners in patients with a fractured neck of femur: A retrospective descriptive cohort study"

- **Travelling Fellowship 1 – $10,000**
  Dr Louis Wang – St Vincent's Health Network Sydney
  "Clinical and Research Fellowship in Cardiovascular Medicine & Cardiovascular Imaging at the Brigham and Women's Hospital, Boston, Massachusetts, USA"

- **Travelling Fellowship 2 – $10,000**
  Dr Roberto Spina – St Vincent's Health Network Sydney
  "Fellowship in structural heart intervention at the New York Presbyterian Hospital/Columbia University Medical Centre, New York, USA"

- **Dr Mayooran Namasivayam – 2017 Clinical Excellence Award – JMO/Registrar - $1,500**
- **Mrs Leanna Woods – 2017 Clinical Excellence Award – Nursing - $1,500**
- **Dr Christine Shiner – 2017 Clinical Excellence Award – Scientist - $1,500**
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