K.01

IN MEMORIAM TO PROFESSOR KEVIN KEALY: PAST, PRESENT AND FUTURE OF DIAGNOSTIC IMAGING

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Abstract

For those who did not know Kevin Kealy, he was a quite remarkable person. He was amazingly talented and charismatic. I first became aware of him in the early hours at Churchill College, Cambridge during the 1976 International Veterinary Association Conference. Kevin, as so often, was at the centre of a group of singing radiologists playing the piano. Our paths crossed many times since then and we worked together on a number of projects. Whenever I was in Ireland, I would always go to visit him at his home.

Kevin was born in Dublin on the 20th of June 1921. After secondary school in Dublin, he attended St Kieran's College Kilkenny, which included six years of seminary training before deciding to embark on a course of veterinary medicine at the Veterinary College of Ireland. Here, he found his true vocation and was awarded numerous medals and awards during his studies. He qualified in 1950 and gained Membership of the Royal College of Veterinary Surgeons in London in the same year.

Kevin spent five years in a mixed, single-handed general practice in Carrickmacross, County Monaghan. In 1955, he was appointed Lecturer in Veterinary Surgery and Obstetrics in the Veterinary College of Ireland. He was awarded a Kellogg Foundation Fellowship in 1957 to study radiology at the University of Pennsylvania for a year. This was to ignite his interest and passion for veterinary radiology. This Fellowship covered a period when veterinary medicine in the North America was far more advanced than in Europe.

Kevin's career oversaw a phenomenal development in veterinary diagnostic imaging. Up and till the early 1960's, veterinary radiology had been used primarily for the investigation of orthopaedic conditions in large and small animals, but with the rapid development of small animal practice, major advances came in the use of radiology for the diagnosis of diseases involving soft tissue. This increased interest in diagnostic radiology amongst veterinarians led in 1963 to the formation of the British Veterinary Radiological Association (BVRA) for which Kevin was co-founder along with amongst others Donald Lawson, Sidney Douglas, and David Williamson. The BVRA subsequently became the European Veterinary Radiological Association as more members joined from mainland Europe and then the European Association of Veterinary Diagnostic Imaging.

In 1968, Kevin hosted the inaugural meeting of the International Veterinary Radiology Association (IVRA) in Dublin. Kevin subsequently became Secretary, President and Director of the IVRA. In 1973, he spent a two-year sabbatical at the veterinary school at Iowa State University as Head of Radiology before returning to Dublin in 1975 to become Head of the Department of Veterinary Surgery.

Kevin published 'Diagnostic Radiology of the Dog and Cat' in 1979. This textbook became a highly successful and was revised through five editions and translated into eight languages. The third and fourth editions were co-authored with his friend and colleague, Hester McAllister and in 2010, the fifth and last edition was additionally co-authored by John Graham. The editions of this textbook chart the huge advances in veterinary diagnostic imaging over Kevin's long and industrious career. The introduction and development of ultrasound as a major diagnostic tool for veterinary practice. The introduction of digital imaging and nuclear medicine and of course, the introduction and development of cross-sectional imaging using CT and MR.

When one looks back over the phenomenal speed and scale of the development diagnostic imaging during Kevin's career, it is hard to see what the next 20, let alone 60 years might bring. Kevin, however, was always optimistic about the future and I am sure he would expect us to embrace these future developments as we have in the past.

K.02

ADVANCED AND THERANOSTIC IMAGING IN THE VETERINARY CANCER PATIENT

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Abstract

Theranostics is the term used to describe the combination of using one radioactive label on a drug to identify (diagnostic) and a second radioactive label on the same drug to deliver targeted radiotherapy (therapeutic) to treat primary tumors and/or metastatic disease. It has also been referred to as 'radiotheranostics', 'radiopharmaceutical therapy', or 'radioligand therapy'. Simplistically, a successful theranostic approach requires a **tumor specific target** (e.g., tumor associated antigen/neoantigen, transporter, other tumor specific characteristic), a **targeting molecule** (e.g., antibody, peptide, small molecule), and a **paired diagnostic and therapeutic radionuclide label** (e.g., 123I/131I, 86Y/90Y, 68Ga/177Lu, 68Ga/ 225Ac, 64Cu/67CU). The field of theranostics has become an important avenue to address patients with metastatic disease, a diagnosis that carries the implication of incurability. The ability to accurately determine the extent and location of metastatic burden with diagnostic radionuclides can be used to determine dosimetry for subsequent therapeutic radionuclides and to assess therapeutic benefit. Further, the ability to determine the relative expression levels of druggable targets within the metastatic burden can be used for prognostic and predictive assessments of targeted therapy as well as help to design rational combination therapy approaches. Advances in diagnostic instrumentation/software in parallel with emerging theranostic pairings, has led to unlimited opportunities, positive impacts on patient outcomes, industry interest and renewed confidence of and in the field.

Theranostic targets include tumor associated antigens (TAA), tumor neoantigens, or tumor microenvironment (TME) antigens/characteristics. TAAs are generally histology-dependent, although some have the potential to target several tumor histologies. Neoantigens are individual-dependent targets and require personalized targeting molecules, making their practicality suspect. Some newly developed theranostic targets are agnostic of histology (e.g., NM600) and hold the potential for the development of "shovel-ready" or "off-the-shelf" theranostics that could be commercially applied to a wider population of cancer patients. Other technologies being explored are approaches that do not rely on tumor produced targets; rather, they rely on forcing tumor cells to express a synthetic target unique to a developed targeting molecule – again, making such approaches agnostic to histology and the individual.

In veterinary companion species, current access to theranostic approaches is limited to the comparative oncologic clinical research setting. Several veterinary groups are actively investigating theranostic advances through the inclusion of relevant parallel patient populations (i.e., pet dogs and cats with spontaneously occurring cancers). Enhanced funding opportunities in both the public and private sectors serve to expand access to clinical benefits in our companion species. From a comparative research standpoint, the physical size, heterogenicity, and spatial distribution of tumors in companion dogs more closely mimic that in humans with cancer. Spatial similarity is critical for studying the

interaction of targeted radionuclide therapy (TRT) with the TME and lymphoid and nonlymphoid organs-at-risk (bone marrow, spleen, thymus, draining lymphatics, kidney, liver, salivary glands). Because of these considerations, dosimetry calculations and adverse event profiles created by including cancer-bearing companion dogs should be more reliable for extrapolation to humans than mouse models. An additional advantage to the inclusion of companion species in theranostic development is the potential to evaluate combination therapies earlier in the development pathway. For example, our group is currently combining theranostic TRT delivered at subablative immunomodulatory doses in combination with external-beam radiation therapy (EBRT) and other immunotherapeutic strategies including intratumoral immunocytokines and immune checkpoint inhibition. Theranostic TRT combined with EBRT in scenarios of oligometastatic and oligo-bulky disease may result in substantial benefit over either technique alone. Examples of such approaches in companion species trials will be discussed.

Several challenges remain in theranostic application including the elusiveness of cure in patients with widespread disease, effect of radiation dose and type (b vs a emitters), target heterogeneity, drug pharmacokinetics, tumor resistance mechanisms (mutational status, immune landscape, DNA repair and damage response), lack of training/facilities, dosimetry methodology, and radionuclide supply problems. Several opportunities exist for the comparative oncology field to contribute to the advancement of theranostic approaches and development of strategies to address these challenges.

Supplemental Reading List:

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K.03

I BLINK THEREFORE I AM: AI AND MEDICINE

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Abstract

If one draws a line that connects Pascal's 17th century calculation machine with Babbage's 19th century computer, the Turing machine, and then ever onwards to the transistor, the microchip, the personal computer, deep learning, machine learning, radiomics and neural nets; one can glimpse a phenomenon hurtling ever faster forwards, exactly as Gordon Moore predicted almost 60 years ago. Nascent superintelligent computing systems and the quantum computing world suggest spectacularly faster and more diverse possibilities in our near future.

Our professional imaging worlds: mine human (one species) and yours, veterinarian medicine (myriad species) have, like so much else in life, been captured by the irresistible gravitational pull of artificial intelligence (A.I.). As we orbit it, we learn to rely upon it and as we do it learns from us and about us. In this lecture, I want to present a personal view of how I see the story so far and our journey ahead. In the same way that gravity shapes Spacetime, our future medical practice will be increasingly shaped by AI. The relative contributions in medicine made by machine and human are inexorably changing as one form of intelligence dances with another.

In only fifty years, scientific opinion has changed from "AI is impossible" and "AI is just automation" to "AI will solve all problems" and "AI may kill us all." Humanity generally and medicine specifically is at an inflexion point. There really is something new under the sun. Artificial intelligence is a new species; the only one created by any other (ourselves) in our known universe. There are many advantages to understanding and nurturing this AI, but one surely is the hope that in due course, it will do the same for us.

K.04

A COMPARATIVE REVIEW OF IMAGING INFLAMMATORY LUNG DISEASE IN PEOPLE AND ANIMALS

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Abstract

The emergence of SARS-CoV-2 in early 2020 prompted an avalanche of scientific research into infectious respiratory disease in people, which consequently highlighted specific differences with veterinary pulmonary imaging.

High Resolution CT (HRCT)

HRCT is most useful for evaluation of chronic airway or interstitial disease and neoplasia. Whilst HRCT is increasingly available in the veterinary context, there is little critical evaluation or research of its role. A 2019 review of veterinary HRCT (Masseau and Reinero) suggests a structured diagnostic approach based on terminology used in human medicine. There is, however, little evidence of the correlation between canine and feline HRCT interpretation and histopathology, immunohistochemistry, and pulmonary functional assessment; so, the adoption of human nomenclature does not fit well.

The differences in pulmonary anatomy between Humans and Dogs and Cats

This presentation reviews the macro and microscopic pulmonary anatomy of Homo sapiens as it relates to HRCT, explaining why human terminology is not always useful in evaluating feline and canine pulmonary CT.

High Resolution CT of the Lung, the 5th edition text by Webb et al, provides an excellent entrée into this field in people. The human lung interstitium includes a pronounced fibrous capsule, which both envelopes the outer lung surface and extends internally like a “skeleton”. It is more prominent and robust than the canine or feline lung interstitium and creates many of the lung HRCT features characterised in people but not identified in dogs and cats. The lack of a secondary pulmonary lobule in dogs and cats also alters lung appearance on CT.

The specific anatomy of the distal human lung shapes how disease appears and contributes to pattern recognition in this species that does not correlate well in dogs and cats. In addition to differences in the fibrous interstitial support network, humans have a distinctly different lymphatic drainage system accounting for the propensity of people to develop pleural effusions after severe, acute peripheral lung disease. Dogs and cats rarely develop pleural effusion with severe inflammatory lung disease, or pleural metastases with pulmonary neoplasia.

Chronic damage to human lungs results in HRCT peripheral honeycombing, traction bronchiectasis and reticular patterns that are not uniformly replicated in feline and canine lungs. The categorisation of HRCT pulmonary micronodules (perilymphatic, centrilobular or random) and septal thickening in people

(linear and reticular opacities) does not translate well to dogs and cats, creating confusion and contributing to the lack of consensus in the approach to interpretation of HRCT in these species. Without a unified approach to canine and feline lung HRCT, veterinarians start from a place of disadvantage, especially without reference to microscopic anatomy, pathophysiology or an understanding of the response of the lung to disease. Two recent veterinary reviews (Reinero C, 2019) highlight some of the challenges in comparing human lung disease to that seen in dogs and cats.

COVID is changing the understanding of human chronic lung disease, and the imaging implications.

The literature documenting the human lung's response to inflammation and infection has exploded in the last three years in response to the pandemic. Despite differences between humans and veterinary patients, there is still much to be learned from lung imaging and deeper understanding of the pathophysiology of lung disease in Homo sapiens. A superb review into the role of cytokines and macrophages in inducing short- and long-term pulmonary damage is worthy of veterinary evaluation (Lee et al), even for veterinary radiologists! Evolution in the use of imaging (CT, MRI and nuclear medicine) has contributed to increased understanding about the human lung's response to severe infection, diffuse alveolar disease, and subsequent lung repair.

This presentation will conclude with a brief outline of how human lung imaging is evolving from morphometric to functional assessment. Electrical impedance tomography (the application of small alternating currents across the thorax to measure the changes of resistance) allows assessment of dynamic tidal variation and lung perfusion and likely has veterinary applications. Functional MRI techniques in people chronical assessment of disease severity and treatment response. As veterinary radiologists, we need awareness of these technologies.

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K.05

EVOLUTIONS, TRENDS, AND CHALLENGES IN EQUINE ULTRASOUND

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Abstract

Ultrasound is a well-established modality in equine clinical practice since several decades.

In the last years, ultrasound has continued to technically advance, extending into higher frequencies and taking advantages from tissues harmonic phenomena and the use of compound imaging. This has led to a better image quality, better contrast resolution and improved tissue interface discrimination in equine ultrasound. Beam steering has been used in musculoskeletal ultrasound (at the enthesis of the suspensory ligament, in the stifle and in the foot) to better distinguish between hypoechoic patterns of pathological value and fibres bundles oriented in a different plane, but also to obtain an orientation of the ultrasound beam perpendicular to the bone for a better assessment of enthesopathies or to better distinguish artefacts form meniscal damage. Ultrawide bandwidth multi-frequency transducers, technology sharpening the ultrasound beam in the elevation direction with continuous focusing and single crystal transducers have provided improved penetration and detail resolution in difficult areas, and more uniform images from near to far field. These technical improvements have led to the obtention of better-quality images in hard-to-image regions and and/or in hard-to image equine patients. Doppler imaging has become routinely used in equine musculoskeletal ultrasound to assess tendons' vascularity. The recent development of microvascular flow imaging ultrasound techniques has increased Doppler sensitivity to detect low flow in small vessels extending the ability of Power Doppler. This can be particularly useful in horses for the assessment of tendon and synovium vascularity. Also, it makes visible normal intratendonous vessels in specific anatomical locations in normal horses, which can be surprising as tendons were essentially avascular while using Color Doppler. It may also increase the rate of positive Doppler results in tendons with sub-clinical B-more abnormalities, especially suspensory branches, as these anatomical structures can already show minimal signal using Power Doppler when they contain sub-clinical B-mode changes.

Parallel to the technological advances in ultrasound, the last 2 decades have seen a tremendous progressive increase in use of Magnetic Resonance Imaging (MRI) to assess musculoskeletal damage in horses, not only in the distal limb but also in other diagnostic challenging areas as the proximal suspensory ligament origin. This fundamental transformation has partially reduced the number of ultrasound examinations of the distal limb, especially of the foot. On the other side, increased portability, and better image quality of affordable portable ultrasound machines (including pocket-size wi-fi transducers) have increased the number of Point-of-care ultrasound (PoCUS) thoracic and abdominal protocols available in horses and their use by equine practitioners and non-radiologist specialists. With these big changes in the equine imaging scenario, it is interesting to explore a new look at the ultrasound examination performed by the imaging specialist. This new look should focus on the values of a high-quality ultrasound examination mainly seen as real-time cognitive practice and challenging the view of ultrasound being "less advanced" than MRI and the comprehensive ultrasound being "superior" to PoCUS in a pyramid of accuracy and/or expertise. In the assessment of the

anatomical regions where an overlap with MRI may exist, ultrasound should be promoted as an easily available complement in selected cases for its real-time abilities (to explore mobility of structures, content of cavities, easily guide interventional procedures…), for the added value of vascular assessment and for its time-efficiency to increase field of view, compare the contralateral limb and follow-up specific accessible lesions. In the assessment of anatomical regions or patients where PoCUS examination is more and more used, PoCUS and comprehensive ultrasound by an imaging specialist should be placed in two parallel trajectories with different strengths, opportunities, and patients.

This presentation will discuss ultrasound developments, their potential clinical impact in equine practice and the evolving role of ultrasound in equine practice.

K.06

CEREBROVASCULAR ACCIDENT - FROM CELL TO PIXEL

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Abstract

The term cerebrovascular disease is defined as any abnormality of the brain resulting from a pathological process compromising its blood supply. Stroke or cerebrovascular accident (CVA) is the most common clinical presentation of cerebrovascular disease and is defined as a clinical syndrome characterized by the abrupt onset of a neurological deficit referable to a specific vascular territory. By convention, these signs must continue for more than 24 hours to qualify for the diagnosis of stroke, which is usually associated with permanent damage to the brain. A transient ischemic attack (TIA) is an acute neurological syndrome of vascular etiology that resolves within 24 hours and often predicts the risk of a significant incoming stroke. CVA are caused by an abrupt disruption of blood flow to the brain owing to blockage of an artery, depriving brain tissue of oxygen and glucose (ischemic stroke), or rupture of a vessel, resulting in hemorrhage into or around the brain (hemorrhagic stroke).

ISCHEMIC STROKE

With limited stores the brain relies on a permanent supply of glucose and oxygen to maintain ionic pump function. When perfusion pressure falls to critical levels, ischemia develops, progressing to infarction if hypoperfusion persists long enough. An infarct is an area of compromised or necrotic brain parenchyma caused by a focal occlusion of one or more blood vessels. It may be caused either by vascular obstruction that develops within the affected vessels (thrombosis) or by obstruction by material that originates from another vascular bed and travels to the brain (thromboembolism).

Depending on the size of vessel involved, infarcts can be the consequence of small-vessel disease (e.g., disease of a superficial or deep perforating artery), which gives rise to a lacunar infarct, or large-vessel disease (disease of a major artery of the brain or its main branches), which gives rise to a territorial infarct. Two distinct regions can be distinguished in ischemic stroke: the core, in which ischemia is severe and infarction develops rapidly; and the penumbra, which surrounds the core and demonstrates a less severe reduction of cerebral blood flow (CBF), so that longer durations of ischemic stress can be tolerated. Magnetic resonance imaging allows diagnosis of ischemic stroke within 12 to 24 hours of the onset and to rule-out other differentials such as haemorrhage or decompensation from primary or metastatic brain tumour. Although infarcts can sometimes be difficult to differentiate from other pathologic processes such as inflammatory diseases, they tend to have certain distinguishing characteristics on conventional MR images.

- Lesion location: typically confined to gray matter, but occasionally white matter involvement if gray matter changes are severe. Suspected to be limited to the vascular territory of a main cerebral artery (rostral cerebral, middle cerebral, caudal cerebral, rostral cerebellar, caudal cerebellar, or one of their respective branches) or a perforating artery (striate arteries,

perforating arteries of the caudal communicating artery, or perforating arteries of the brainstem) with resultant sharp demarcation from the surrounding normal brain tissue
- Appearance: well-defined, sharply demarcated from adjacent brain parenchyma with homogenous appearance
- Signal intensity: hyperintense on T2-weighted and/or FLAIR
- Mass effect: minimal or none
- Contrast-enhancement: more often within 7 days [24hrs – 8 weeks] and associated with reperfusion
- Restrictive on ADC in the first 10 to 14 days.

HEMORRHAGIC STROKE

In hemorrhagic stroke blood leaks from the vessel directly into the brain, forming a hematoma within the brain parenchyma, or into the subarachnoid space.

The MR signal intensity of intracranial haemorrhage is influenced by several intrinsic (time from ictus, source, size and location of haemorrhage) and extrinsic (pulse sequence and field strength) factors.

As the hematoma ages, oxyhemoglobin in blood sequentially breaks down into several paramagnetic products – first deoxyhemoglobin, followed by methemoglobin, and, finally, hemosiderin.

The temporal progression of the signal intensities during hematoma occurs as expected and in a centripetal fashion (outer part being the older and inner part being the newer) with no delay in the transition between the blood-breakdown products. This characteristic is key in differentiating intra-axial hematoma from hemorrhagic malignant neoplasia.