EMJ RADIOLOGY

European Edition — Vol. 1.1 September 2020 emjreviews.com

+ ECR ANNUAL MEETING 2020

Reviewed

+ INTERVIEWS

Three influential members of the European Society of Radiology (ESR) discuss their positions within the society and provide insight into their areas of expertise.

+ ABSTRACT REVIEWS

Reviews of abstracts presented at ECR 2020 covering topics such as low-grade glioma diagnosis, radiography student motivation, and radiomic workflow.

+ EDITOR'S PICK

Regulatory and Ethical Issues in the New Era of Radiomics and Radiogenomics

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"Thousands of posters were presented, and hundreds of presentations delivered, the breaking news from which are collated in our review of the congress"

Spencer Gore, CEO

+ ARTICLES

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EMJ Radiology 1.1

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Welcome

Dear Readers,

Welcome to the inaugural issue of *EMJ Radiology*. This open-access eJournal covers the most important developments in radiology through interviews and articles from experts within the field and a congress review presenting the highlights from the European Congress of Radiology (ECR) Annual Meeting.

Despite the ongoing COVID-19 pandemic, the European Society of Radiology (ESR) held another premier meeting, but this time virtually. Thousands of posters were presented, and hundreds of presentations delivered, the breaking news from which are collated in our review of the congress. Summaries of key abstracts presented at the congress are also included and are written by the presenters themselves, covering topics such as radiomics in CT imaging texture analysis and imaging in glioma diagnosis.

One of the main themes of the congress this year was artificial intelligence and its role in radiology. While radiology is a discipline that is embracing the technology, the risks, ethics, and data bias are considerations that were hotly discussed at this year's meeting. Included in our congress review is a summary of an ECR session that discussed these controversies and the future of artificial intelligence in radiography.

In complement to the ECR content, we spoke with three key members of ESR: Dr Adrian Brady, Previous Chair of the ESR Quality, Safety & Standards (QSS) Committee and ESR 2nd Vice-President; Prof Valérie Vilgrain, Director of the European School of Radiology (ESOR); and Prof Nandita de Souza, Chairperson of the European Imaging Biomarkers Alliance – EIBALL. The interviewees spoke about their position at the society and research interests and provided insight into their expertise in radiology.

Articles included in this issue present the latest developments in the field. Pesapane delves into the regulatory and ethical issues of radiomics and radiogenomics, Morales et al. explore the use of three-dimensional ultrasound for the detection of endometrial cancer, Nguyen et al. present the latest technologies in placental imaging, and Rasoaherinomenjanahary et al. highlight the role of imaging in retained foreign bodies after surgery.

I would like to take this moment to thank all the contributors and Editorial Board for their help in creating this special eJournal.

Spencer Gore

Chief Executive Officer, EMG-Health

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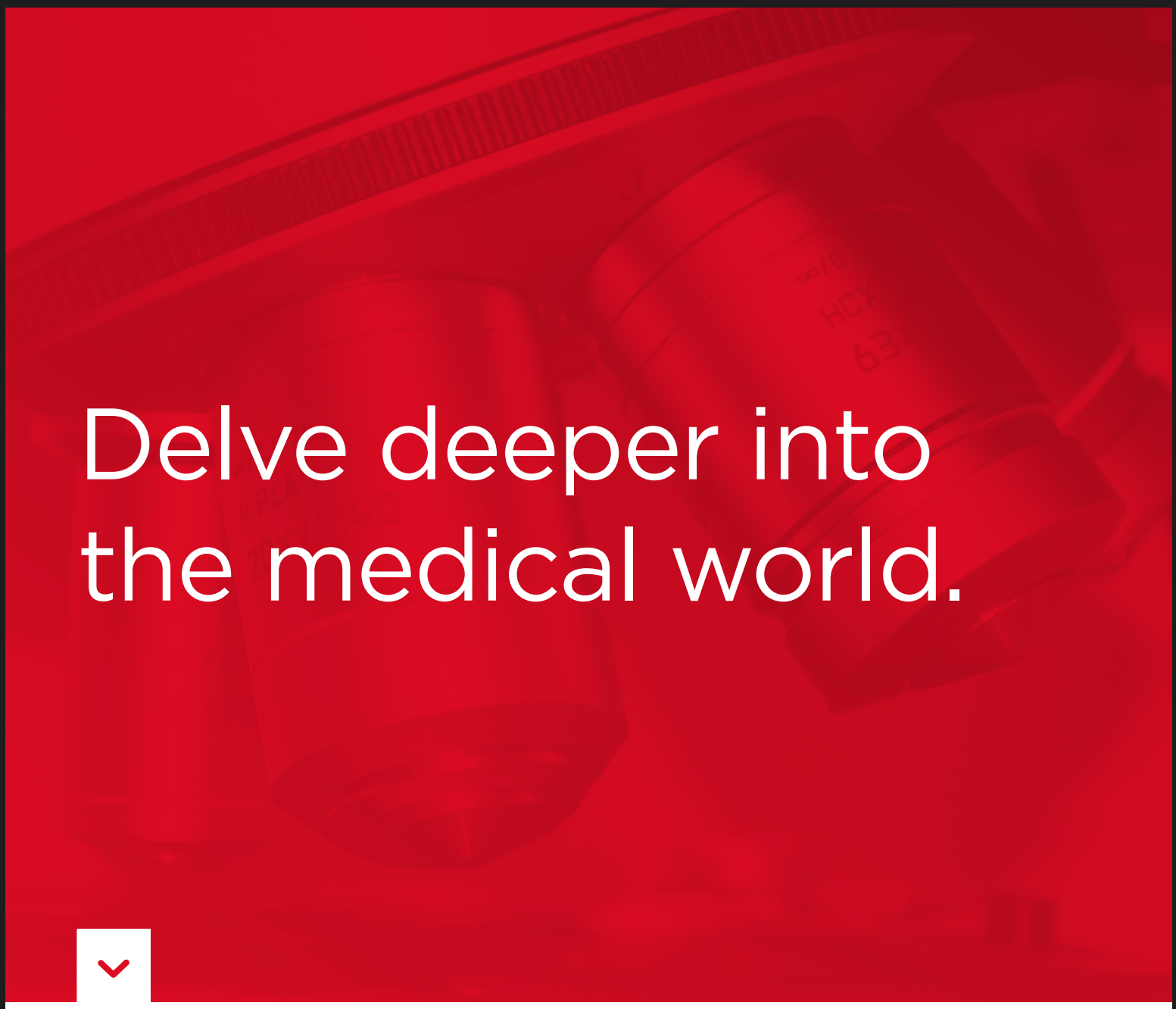

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Foreword

Dear Readers,

It is a great pleasure for me to welcome you to the first issue of *EMJ Radiology*, an open-access eJournal bringing you the latest developments in the field. Collaboration is an integral component of progress in scientific, medical, and the allied healthcare professions (diagnostic and therapeutic radiographers).

The collaboration and resilience that all healthcare professionals, scientists, and researchers have demonstrated over this demanding year due to COVID-19 has been inspirational. Adapting to the ongoing pandemic, the European Society of Radiology (ESR) delivered their first fully online European Congress of Radiology (ECR).

This online event brought together professionals with a special interest in topics related to radiology from around the world to discuss and present research, and, importantly, build a sense of community and network. Highlights from the event plus a review of an ECR session on artificial intelligence in radiography can be found in the congress review section.

Alongside the coverage of ECR, there are interviews with key members of the ESR, who provide a unique insight into their fields of expertise which include artificial intelligence, imaging biomarkers, high-intensity focused ultrasound, and much, much more.

This issue reflects a wide range of specialities in radiology, including ethics of radiomics and radiogenomics, three-dimensional ultrasound in ovarian cancer detection, and new imaging technologies for placental imaging.

The paper that I have selected as the Editor's Pick highlights the synergistic relationship between computer technology, imaging, and genetics of disease and discusses the legal and ethical questions that need to be addressed because as technology evolves, so does the need for cybersecurity and data protection.

I hope you all enjoy reading *EMJ Radiology*, an issue that I believe to be of interest to a wide range of healthcare professionals, including radiologists, diagnostic radiographers, and therapeutic radiographers.

Yasmeen Malik

Senior Lecturer, St George's University of London, UK

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Congress Review

Review of the European Congress of Radiology (ECR) Annual Meeting 2020

Location: ECR 2020

Date: 15th – 19th July 2020

Citation: EMJ Radiol. 2020;1[1]:10-22. Congress Review.

This year, the European Congress of Radiology (ECR) took place online for the first time as a result of the ongoing coronavirus disease (COVID-19) pandemic. Over the 5-day scientific programme, there were 50 streamed sessions and over 1,800 abstract and poster presentations, with more than 200 virtual booths available to visit at the event. During the opening ceremony, Prof Boris Brkljačić, Chairman of the European Society of Radiology (ESR), announced that due to not having the usual time constraints of a physical congress, ECR 2020 will continue from July through to the end of December in the form of Highlight Weeks, each dedicated to a certain subspecialty or theme. On the decision to hold ECR 2020 online, Prof Brkljačić said: "Adaptation and innovation have always been strengths of the ESR, and having already established itself as a leader in online education over the past few years, the society rose to the challenge and made the decision to transform ECR 2020 into a fully online congress."

The opening ceremony, like the entirety of the congress, captured the atmosphere of an onsite meeting. Prof Brkljačić welcomed attendees and thanked all radiographers and radiologists on the frontline of the pandemic, adding: "Your dedication for caring for patients, even when putting yourself at risk, is the strongest example of the compassion, understanding, and love that lies at the core of our professions." Contributing to the progression of knowledge on COVID-19, the ESR have continually released educational resources and dedicated four sessions at ECR to the disease.

The theme of connecting science with art was present throughout the opening ceremony, with Prof Brkljačić drawing comparisons between the congress and Adagio in G Minor by Tomaso Albinoni, arguably one of the most famous pieces of classical music: "The spirit of this beautiful work is really in its sense of calm. This is the essence of Adagio, and that is our guiding philosophy for this year's congress. To take a step back and think differently."

"Your dedication for caring for patients, even when putting yourself at risk, is the strongest example of the compassion, understanding, and love that lies at the core of our professions."

Award winners were then announced, each preceded by their choice of music with a special significance to them, in a rendition by a four-piece band. ESR Honorary Membership was awarded to Prof Danta R. Casale Menier, Prof Yi-Hong Chou, and Prof Valerie P. Jackson, in recognition of their scientific excellence, international reputation, and achievements in national or international organisations. This year, Prof Richard FitzGerald, Prof Jim A. Reekers, and Prof Katrine Riklund received Gold Medals as acknowledgement for being outstanding scientists in the field of radiology or an allied science.

The plenary sessions were delivered by Prof Marie-Pierre Revel, in which the lessons and questions from the COVID-19 pandemic were considered; Prof Valérie Vilgrain, who discussed the resilience of the liver; Dr Bernd Montag, in which the movement towards digitalised healthcare was presented; and Prof Nenad Šestan, who detailed the formation of neural circuits.

Daily Table Talks took place throughout the congress, which were hosted by Prof Brkljačić and ESR Past President Prof Lorenzo Derchi. In these sessions, special guests were invited to discuss the scientific programme and current challenges in radiology, including clinical audits, lung cancer screening, and the special theme of Children in Focus.

This one-of-a-kind congress was truly spectacular, and, to quote Prof Brkljačić, "can only be described as a congress of the future." We look forward to being able to attend what will surely be another great meeting next year in Vienna, Austria; until then, please enjoy the following review of the ECR 2020 Online Meeting.

ECR 2020 REVIEWED →

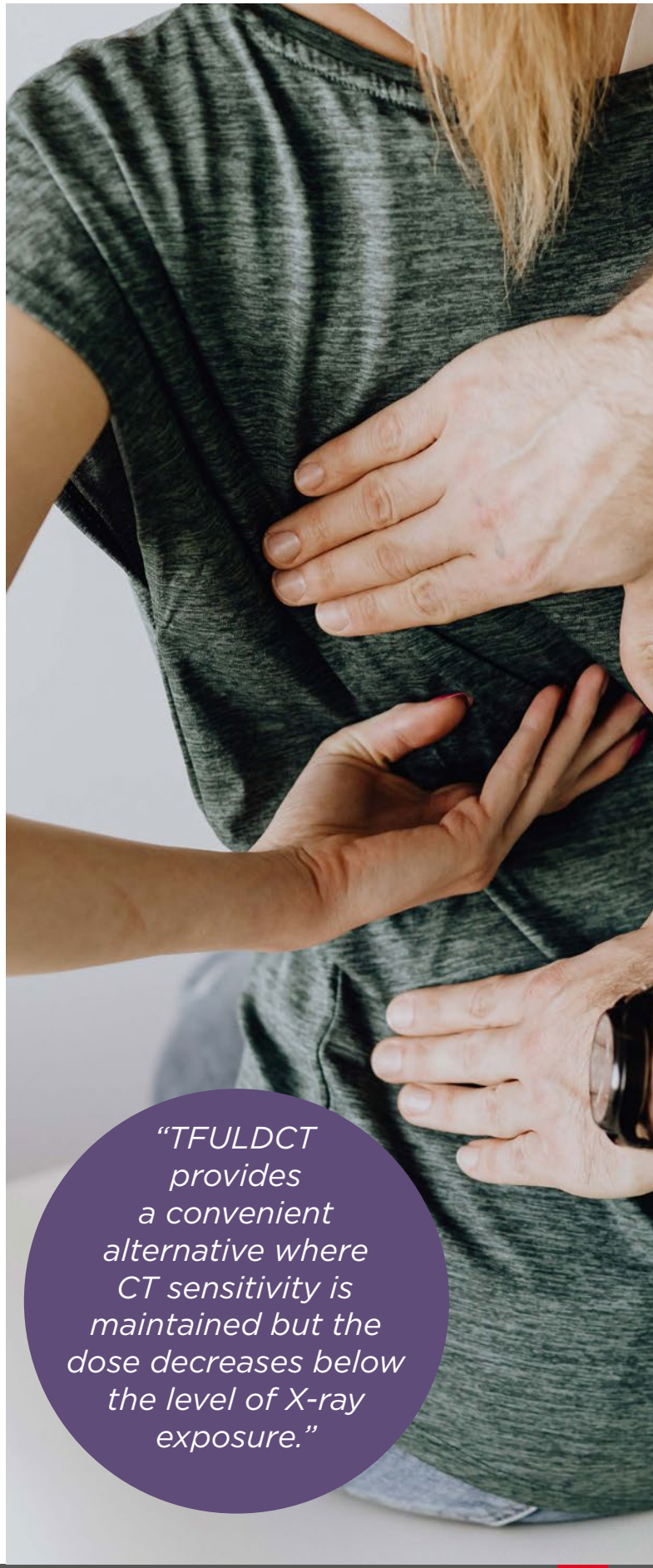
Tin Filtration Reduces CT Dose and Improves Sacroiliitis Diagnosis

TIN FILTRATION can dramatically reduce radiation dose and therefore radiation exposure, which is in line with the 'as low as reasonably achievable' (ALARA) principle. One possible application of this technique is for confirmation of sacroiliitis diagnosis. In a study investigating tin filtrated ultra-low-dose CT (TFULDCT) in examining sacroiliac joints (SIJ) for sacroiliitis, it was shown that TFULDCT can more accurately identify whether inflammatory rheumatoid disease is present in SIJ joints compared with X-ray. Results from this study were presented at ECR 2020, and in an ECR Today news story.

CT is commonly used in diagnostic algorithms, and adherence to the ALARA principle is often achieved by restricting the extent of exposure, adapting scanning parameters, and adjusting images post-process. Tin filtration is another approach that can be taken; this reduces radiation dose by filtering low-energy photons, which are responsible for image contrast and noise reduction, between the X-ray generator and patient. The resultant reduction in radiation dose comes with the disadvantage of reduced image contrast and increased noise, limiting the use of tin filtration to distinguishing structures with significantly different densities.

In the pilot study, effective radiation doses and diagnostic usefulness of TFULDCT (median dose: 0.11 mSv) and X-ray (median dose: 0.25 mSv) were evaluated. The TSULDCT and X-ray images were independently evaluated by three radiologists, and findings were decided to be either clearly positive, clearly negative, or uncertain for the diagnosis of sacroiliitis. The results showed that TRULDCT had a significantly better overall diagnostic benefit than X-ray (80% versus 30%, respectively).

Lead author Dr Eva Korčáková, University Hospital in Pilsen, Pilsen, Czech Republic, commented: "Our results confirm that TFULDCT is able to more accurately decide the presence or absence of inflammatory rheumatoid disease of SIJ compared to X-ray." She added that: "TFULDCT provides a convenient alternative where CT sensitivity is maintained but the dose decreases below the level of X-ray exposure."



"TFULDCT provides a convenient alternative where CT sensitivity is maintained but the dose decreases below the level of X-ray exposure."

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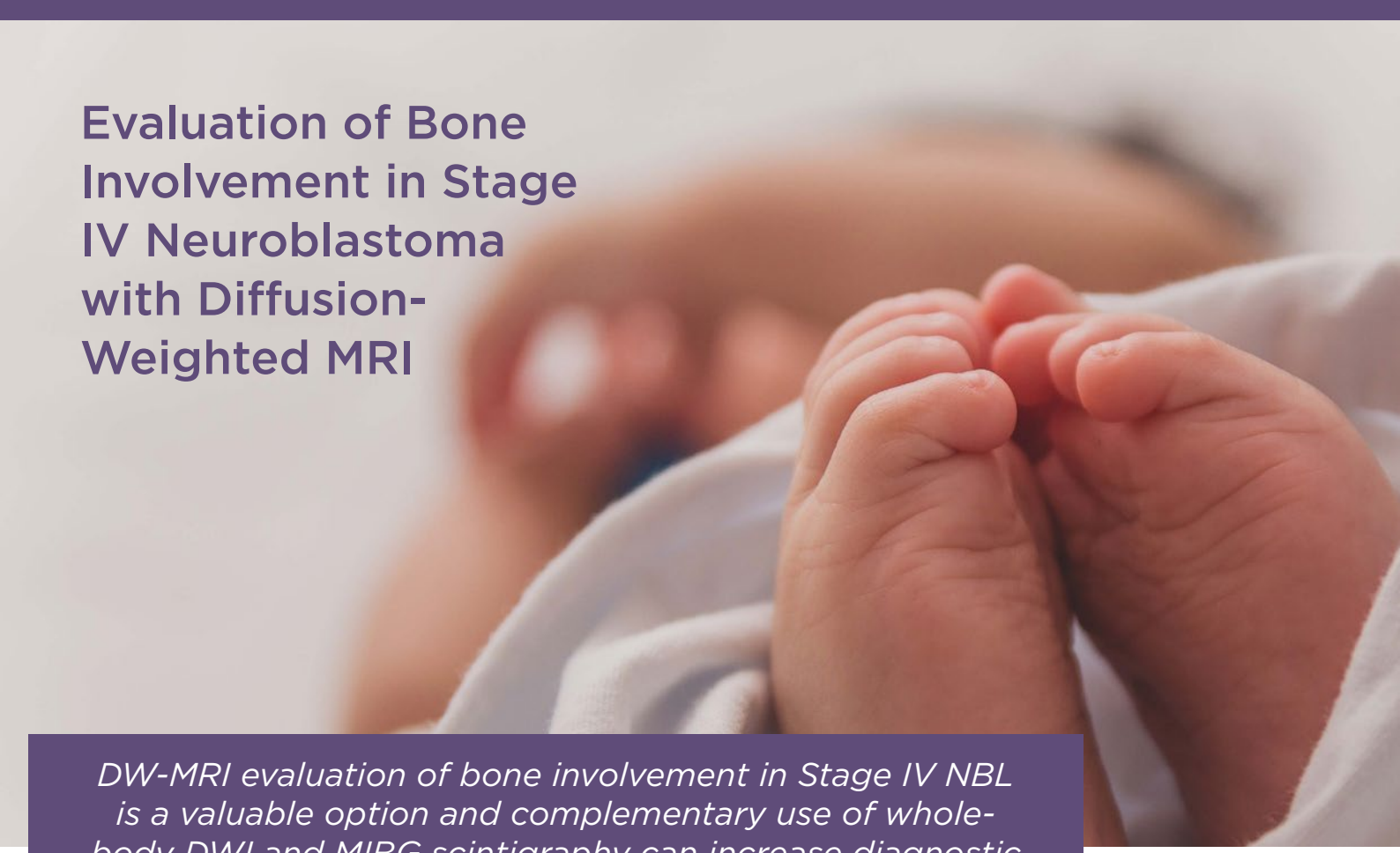
Evaluation of Bone Involvement in Stage IV Neuroblastoma with Diffusion-Weighted MRI



DW-MRI evaluation of bone involvement in Stage IV NBL is a valuable option and complementary use of whole-body DWI and MIBG scintigraphy can increase diagnostic accuracy in the evaluation of bone involvement.

MANAGEMENT of patients with Stage IV neuroblastoma (NBL) requires accurate evaluation of metastatic bone disease including assessment of response to chemotherapy. Diagnosis with radiolabelled metaiodobenzylguanidine (MIBG) imaging is currently the gold standard; however, according to new research presented at ECR 2020, active metastatic bone lesions that are depicted on MIBG imaging are also evident on diffusion-weighted (DW) MRI, previously considered a limitation of MRI.

Here, researchers at SJD Barcelona Children's Hospital, Barcelona, Spain, hypothesised whether MRI could detect bone involvement in NBL and if quantitative DW-MRI imaging is able to differentiate non-viable lesions from viable tumours.

In the retrospective study, 18 patients were recruited to compare whole-body DW-MRI and MIBG to assess the presence of metastatic osseous lesions in patients with Stage IV NBL who had received conventional chemotherapy. Results demonstrated a total of 171 lesions on all 18 patients. On MIBG, 73 bone lesions were reported as positive and nine MIBG bone lesions were not represented on DW-MRI. Coincidence between DW-MRI and MIBG was observed in 62 lesions and a statistically significant correlation was established between MIBG-positive bone lesions and a lower apparent diffusion coefficient value on DW-MRI.

Th evaluation of bone involvement in paediatric NBL has been considered a limitation of MRI because of its inability to differentiate between viable tumour and nonviable residual lesions. This is the first study comparing MIBG and DW-MRI in the evaluation of bone metastatic disease in paediatric NBL and results presented here suggest that active metastatic bone lesions that are depicted on MIBG imaging are also evident on DW-MRI and show restricted diffusion compared to 'residual' bone lesions that are not evident on MIBG.

While MIGB is the gold standard for the diagnosis of NBL, with a sensitivity and specificity of 90% and 100%, respectively, DW-MRI evaluation of bone involvement in Stage IV NBL is a valuable option and complementary use of whole-body DWI and MIBG scintigraphy can increase diagnostic accuracy in the evaluation of bone involvement.

Predicting Fetal Lung Maturity with a Noninvasive Technique

NONINVASIVE sonographic techniques can be used to predict and evaluate fetal lung maturity. This is according to the results from a new study presented at ECR 2020, and in an ECR Today news story.

In the Minia University Maternity and Children's Hospital in Minia, Egypt, 40 females between 28 and 40 weeks of gestation were enrolled in an observational prospective cohort study that used main pulmonary artery Doppler measurements to predict fetal lung maturity. In Egypt, approximately 7.3% of all live births are premature. Respiratory distress syndrome is a significant complication of prematurity and the most common cause of respiratory distress in premature infants, strongly associated with structural and functional immaturity of the lungs. This lack of full maturity in the lungs is the most common cause of death in neonates.

The risk of respiratory distress syndrome in infants can be predicted with the use of biochemical tests such as the lecithin/sphingomyelin ratio, which require invasive amniocentesis. Lung volume measurement, gestational age, epiphysis centres, placental grading, and estimated fetal weight are noninvasive methods that use ultrasound to evaluate fetal lung maturity but thus far, the techniques have not achieved success. The authors of the study aimed to explore alternative noninvasive ultrasound techniques for fetal lung maturity assessment using quantitative ultrasound texture analysis and pulmonary artery Doppler.

The main pulmonary artery Doppler diagnostic measurements included pulsatility index, resistance index, and acceleration time/ejection time, the accuracy for which was tested comparing clinical outcomes with the Doppler findings. Neonatal respiratory distress syndrome was diagnosed in nine fetuses (22%) and there was a significant correlation between low acceleration time/ejection time and respiratory distress syndrome development. The authors concluded that a noninvasive fetal lung maturity test and fetal pulmonary artery acceleration time/ejection time ratio are of similar effectiveness for predicting fetal lung maturity.

Respiratory distress syndrome is a significant complication of prematurity and the most common cause of respiratory distress in premature infants, strongly associated with structural and functional immaturity of the lungs.

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How to Manage Patient 'No-Show' in Radiology Departments

PREPROCEDURAL preparation is essential for nuclear medicine departments, and patient no-show, where patients do not turn up for their scheduled appointment, has a large impact on the productivity of hospitals. In an abstract presented at ECR 2020, results from a study in Doha showed the impacts no-show has on hospitals, and how to negate these.

Patient no-show is problematic for all hospital departments, and for radiology departments causes the issue of nonreusable radioactive material wastage, such as technetium 99m (Tc-99m), which ultimately leads to significant financial loss to the hospital.

In the study, between January and February 2019 loss to the hospital in terms of finance and time was calculated, based on the orders of Tc-99m and other radiopharmaceuticals and the length of appointments. A total of 84 out of 499 appointments were reported as no-shows during the 2-month study period. This 17% no-show rate caused a loss to the hospital of $39,000 USD and 864 hours wasted.

Reasons for no-show included illness, lack of transport, surgery, death in the family, or another appointment. The authors thereby decided to focus on patient education regarding the negative effects this has on the hospital, as well as an option to choose a preferred appointment date, rather than being assigned one by hospital staff. Additionally, the authors noticed that the no-show percentage reached as high as 22%, and suggested that a stricter no-show policy, such as a monetary deposit that is nonrefundable upon no-show, be implemented.

Following the distribution of educational leaflets, assignment of appointments according to patient preference, and hospital staff emphasis of the harmful impacts of missed appointments, the no-show percentage reduced to 13% (-4%).

The authors advocated for continuous training and education on the negative effects of patient no-show by hospital staff, improved communication skills training to receptionists, and use of emails as reminders. It is hoped that these changes will result in less financial loss to the hospital and shorter waiting times.

This 17% no-show rate caused a loss to the hospital of $39,000 USD and 864 hours wasted.

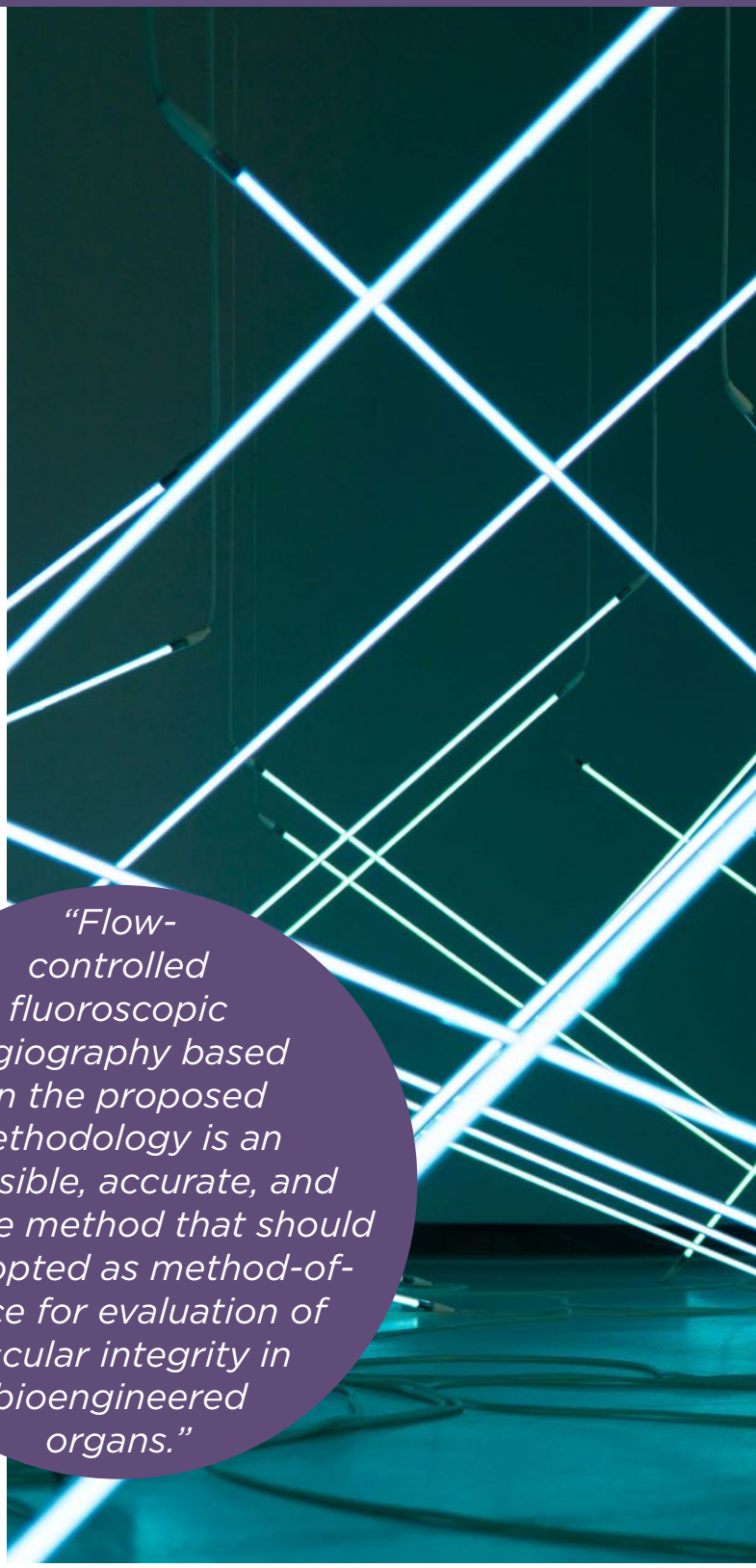
Angiography Assesses Effects of Decellularisation on Renal Transplants

FLUOROSCOPIC angiogram could be an important step in determining the transplant-readiness of decellularised kidneys. An Israeli study, presented at ECR 2020, has identified the value of the procedure to assess both vascular patency and perfusion following decellularisation.

Decellularised kidneys have had their cellular content removed, preserving the extracellular matrix and microstructures, biochemical composition, and cell-instructive signals, through a process of whole organ perfusion decellularisation. The intent of this technique is to remove immunogenic components so that transplant tissues can be available to any recipient, regardless of donor match. The technique relies on intact vasculature to circulate detergent-based solutions that dissolve cells and remove cellular antigens and DNA.

A study at a major transplant centre in Israel assessed the value of fluoroscopic angiography to reliably determine the integrity of arteries and veins of porcine kidneys, both pre- and postdecellularisation. Controlled flow conditions were used during fluoroscopic angiography to gauge vasculature patency and permeability via measurement of contrast media greyscale intensity and washout index.

The *ex vivo* angiograms revealed no difference in vessel patency following decellularisation, but did show significantly lower washout index in the porcine kidneys following the decellularisation process. The study identified delayed contrast clearance and increased vascular permeability, as well as evidence of extravasation of the contrast media into the kidney parenchyma. These changes were only evident in the kidneys following decellularisation.



"Flow-controlled fluoroscopic angiography based on the proposed methodology is an accessible, accurate, and sensitive method that should be adopted as method-of-choice for evaluation of vascular integrity in bioengineered organs."

The researchers undertaking the study, in a collaboration between the Department of Organ Transplant and Department of Radiology, Rabin Medical Center, Petah Tikva, Israel, highlighted the importance of these findings to the progress of developing bioengineered transplant organs: "Flow-controlled fluoroscopic angiography based on the proposed methodology is an accessible, accurate, and sensitive method that should be adopted as method-of-choice for evaluation of vascular integrity in bioengineered organs."

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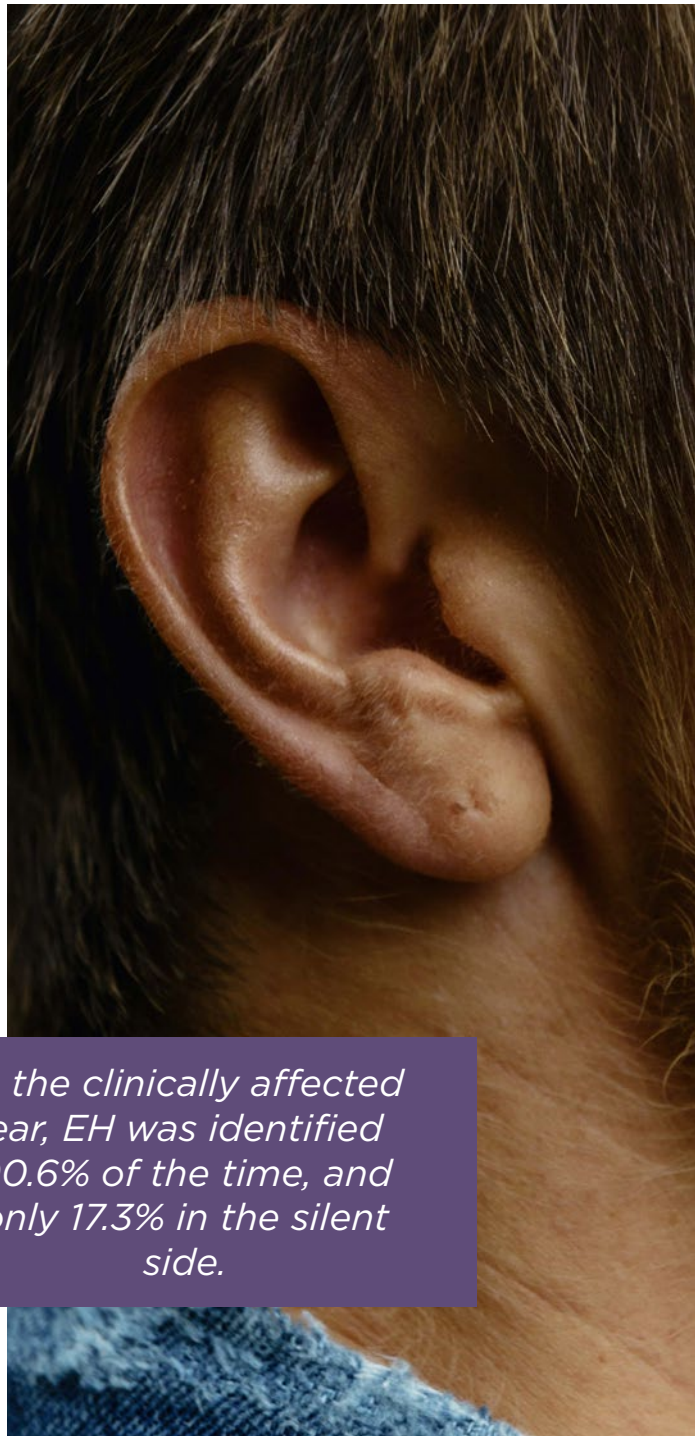
Advancements in MRI Includes Grading Scale for Endolymphatic Hydrops

ENDOLYMPHATIC hydrops (EH) is the dilation of the endolymphatic section in the inner ear and compartments of the perilymphatic space. It occurs in inner-ear diseases and is acknowledged as the anatomical and pathological indicator of Ménière's disease, a chronic condition with hallmark fluctuating low-frequency hearing loss, vertigo, tinnitus, and blockage sensations in the ear.

Autopsy, rarely carried out for inner ear pathology, was previously the only known method for EH diagnosis; therefore, research into Ménière's disease and EH has been limited. Authors of a novel study from Pamplona, Spain, used information from patients with unilateral definite Ménière's disease and aimed to evaluate the degree of interobserver similarities in both the detection and grading of EH in the cochlea and vestibule. The results for this study were presented at ECR 2020 and shared in an ECR Today news story.

In the study, vestibular EH was evaluated in 75 patients with diagnosed unilateral definite Ménière's disease using cisternography, T2-FLAIR, and REAL IR imaging. In the clinically affected ear, EH was identified 90.6% of the time, and only 17.3% in the silent side. Three different visual scales to evaluate vestibular EH were compared: 4 stage, none/mild/moderate/severe; 3 stage, none/moderate/severe; and 2 stage, none/present. The researchers found that a 4-stage vestibular EH grading system provided the best interobserver consistency.



In the clinically affected ear, EH was identified 90.6% of the time, and only 17.3% in the silent side.

Of late, MRI has advanced significantly and is able to provide assessment *in vivo* of EH. The testing methods have been thoroughly researched and are now being implemented in the clinical field and will soon be utilised within radiology hospital departments. Studies thus far have investigated the validation and evaluation of treatment response in patients with Ménière's disease by looking into the correlation between findings of MRI EH and clinical and cochleovestibular tests. The different scales for EH grading used in these studies prevent effect reproduction and comparability between studies, highlighting the importance of this novel study in determining the relationship between data in clinical studies. With this information, future research could establish the recommended scale for EH scale and provide clarity on study differences.

Cost-Effective Strategies for Solitary Pulmonary Nodule Diagnosis

SOLITARY pulmonary nodule (SPN) diagnostic accuracy is important because if early-stage lung cancer is treated with curative intent, the 5-year survival rates can be up to 70%. The diagnostic challenge associated with this is that not all SPN are a result of lung cancer, and accurate characterisation of the SNP can be expensive and inaccessible. However, dynamic contrast-enhanced CT (DCE-CT) has shown to be accurate and cost-effective, as presented in an abstract at ECR 2020 and in an ECR Today news story.

Nodule size is associated with the risk of malignancy, and thus directs the use of current management strategies. No follow-up is required for nodules <5 mm, but PET/CT or biopsy are used for further investigation of nodules >8 mm. In addition to the expensive costs associated with PET/CT and biopsy, access to PET/CT can be limited as it is not uniformly available at all hospitals.

In the large, multicentre trial, 312 patients with an SNP sized 8–30 mm were recruited across 16 hospitals in the UK. The participants underwent both PET/CT and DCE-CT, and biopsy/surgical resection or stability over the 2-years follow-up imaging period were used to determine final diagnosis of the nodule. DCE-CT uses intravenous iodine-based contrast to quantify the degree of enhancement of the nodules, which represents the vascularity, a highly sensitive and moderately specific marker for SPN. However, the trial concluded that PET/CT is more accurate for SNP diagnosis, but DCE-CT is more cost effective.

When the investigators explored 'willingness to pay' per correctly treated malignancy, DCE-CT was the preferred strategy when below £9,000 (€10,700). However, a combination of DCE-CT and PET/CT became the most-likely cost-effective strategy (probability equal to one) when society's willingness to pay to get one more correctly treated malignancy was increased to £16,000 (€19,000). Authors of the study Prof Fiona Gilbert and Dr Jonathan Weir-McCall from the University of Cambridge, Cambridge, UK, noted: "These findings have significant implications, especially in light of the introduction of CT-based lung cancer screening."

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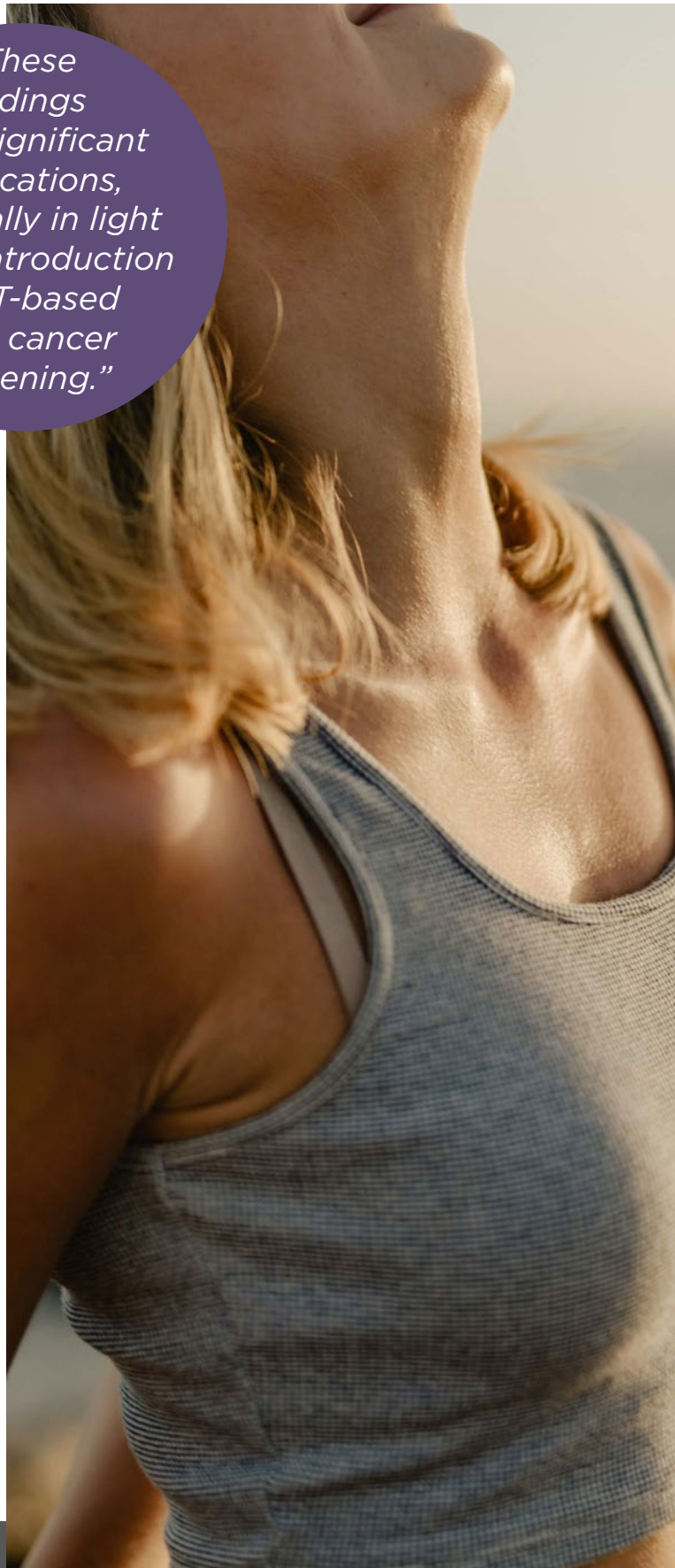

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Radiation Dose Optimisation for Paediatric Chest Radiography

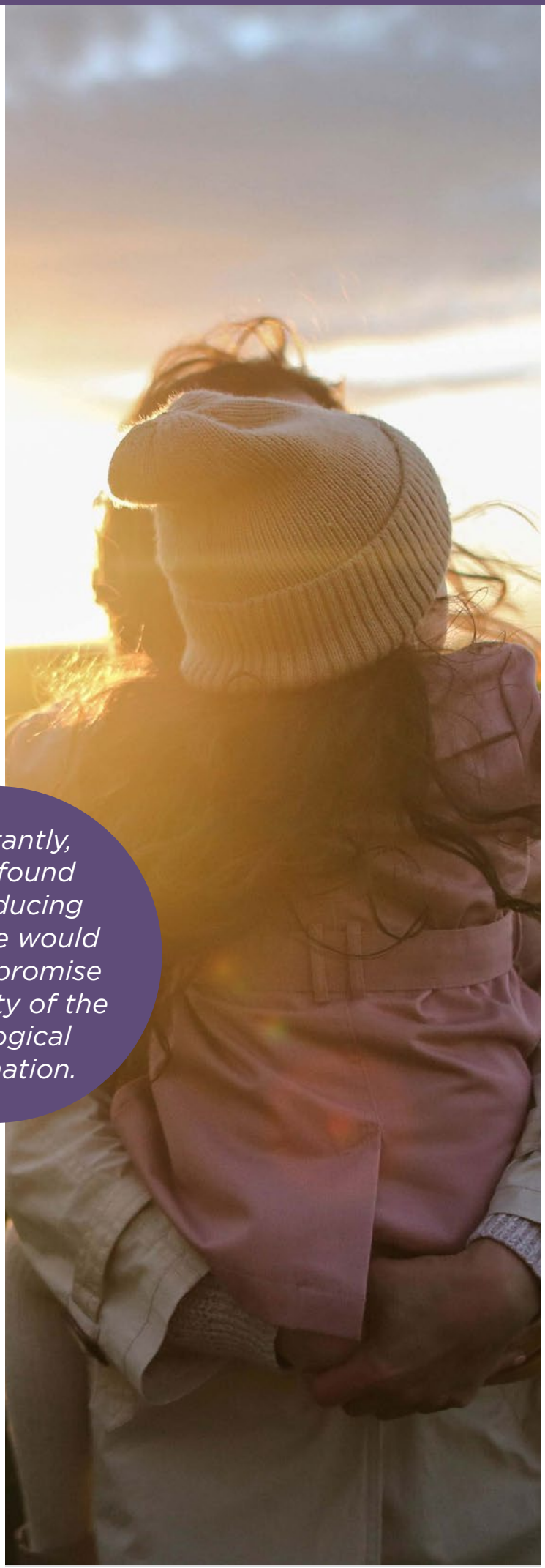
EXPOSURE to ionising radiation has been shown to generate a higher relative risk of leukaemia and brain, skin, thyroid, and breast cancer in children. Chest radiography is the most requested radiographical examination in paediatric patients (0–18 years old), and although it has a reasonably low exposure dose, a study presented at ECR 2020 sought to establish radiological exposure protocols for chest radiographs for this patient population, to reduce unnecessary exposure.

The study involved three steps: optimisation tests, quality evaluation, and clinical application. Variables that were accounted for included age, weight, height, projection of the exam, tube potential, exposure time, use of automatic exposure control, use of an anti-scatter grid, focus-detector distance, and kerma-area product. A sample of 44 examinations, 59.1% of which were male, were analysed, and the children were classified by weight.

Importantly, it was found that reducing exposure would not compromise the quality of the radiological examination.

Dose reductions dependant on weight class were applied using the protocol, which led to a 60% relevance for Class 2 (<5 kg), 75% for Class 3 (5–15 kg), 59% for Class 4 (30–50 kg), and 54% for Class 5 (50–80 kg). Statistical significance was reported both before and after optimisation and was significant for all weight classes.

Importantly, it was found that reducing exposure would not compromise the quality of the radiological examination. These results will guide clinicians in implementing an optimised cycle of the most frequently used radiographic examinations in paediatric patients, to minimise the harmful effects associated with diagnostic tests and therapeutic procedures that utilise ionising radiation.



Nanoparticles Make Microfractures Easily Visible on CT Images

MICROFRACTURES in bones can be difficult to detect due to the dense abundance of calcium in the bone, but if left untreated, they can develop into a complete bone fracture. In study results presented at ECR 2020 and summarised in an ECR Today news story, researchers showed that targeted nanoparticles could make microfractures profoundly visible.

Conventional CT cannot be used to identify microfractures due to the spatial resolution being approximately 0.500–0.625mm, and thus not allowing the detection of damage at the micrometre level; therefore, X-ray imaging-based techniques are normally used.

In the study, the researchers introduced colour to X-ray images using targeted nanoparticles comprising K-edge metals that are chemically 'trained' to locate microfractures, which then become visible with CT imaging. These particles differentially bind to the calcium in the microcracks, and, based on their distinctive K-edge energies, can be quantified using photon counting.

The K-edge nanoparticles accumulate in the microfractures and colourised voxels on the background of grey-scale X-ray are produced, allowing the identification of these contrast-enhanced targets. The researchers utilised MARS spectral CT technology equipped with Medipix detectors and MARS photon counting CT, and the resultant images discriminated microfractures from healthy bone with unparalleled clarity.

"Together with these clinically translatable ligand-directed particles, MARS can generate images that reveal abnormalities that usually remain undetected by conventional methods," summarised Dr Dipanjan Pan, one of the researchers involved in the study, University of Illinois at Urbana-Champaign, Illinois, USA, and University of Maryland, Maryland, Baltimore, USA.

"Together with these clinically translatable ligand-directed particles, MARS can generate images that reveal abnormalities that usually remain undetected by conventional methods"

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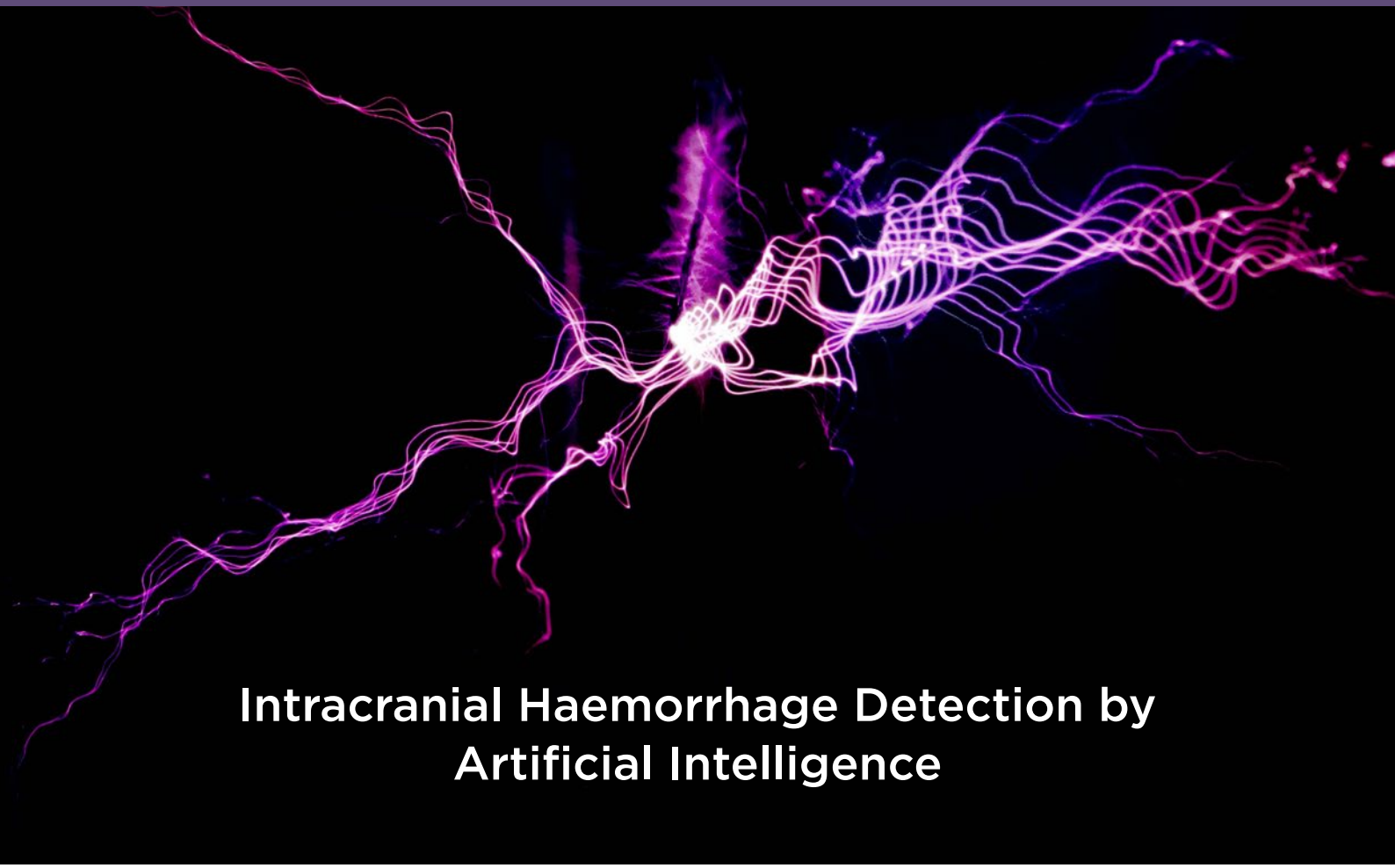

Intracranial Haemorrhage Detection by Artificial Intelligence

ARTIFICIAL intelligence (AI) supports on-call residents in detecting intracranial haemorrhage (ICH) at the emergency department of the Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium. Here, the radiology workflow integrated an automated triage system which prioritises critical cases, based on the patient's severity and urgency, ensuring that these patients are treated first. The data from this research were presented at ECR 2020 and summarised in an ECR Today news story.

To assess the performance of an AI tool using a deep learning algorithm for the detection of ICH on head CT exams with clinical workflow integration, researchers at UZ Brussel collected a dataset of 500 consecutive CT exams and their clinical reports between 1st September and 1st October 2019. CT exams were transferred for ICH detection by an AI tool, and the number of successfully processed studies by the AI were registered and the diagnostic performance, sensitivity, and specificity were calculated.

During the 1-month implementation phase, reports for 338 studies (77.6%) were generated by the algorithm and 22.4% failed, most likely because of technical issues. From these 388 studies, the AI tool labelled 31 (7.9%) as having ICH while the expert readers detected 37 (9.5%) with ICH. ICH detection between AI and expert readings was considered to be similar, and the algorithms performance revealed a 98% negative predictive value, 61% positive predictive value, and a sensitivity and specificity of 84%.

"This is an opportunity to leverage the power of AI to shape the radiologists of the future."

Dr Nina Watté, UZ Brussel, noted: "AI could automatically evaluate three-quarters of all head CT exams. With high specificity and negative predictive value, the AI tool shows the potential to rule out ICH, helping radiologists select which scans need to be viewed less urgently."

The potential for AI to support the selection of imaging modalities, diagnoses, and even in communication with colleagues and patients is vast. Looking forward, Dr Watté concluded: "This is an opportunity to leverage the power of AI to shape the radiologists of the future."

Artificial Intelligence and the Future of Radiography

Katherine Colvin
Editorial Assistant

Citation: EMJ Radiol. 2020;1[1]:23-25.

EVOLUTION of technology, global availability of massive volumes of data, and progress in evidence-based clinical care have contributed to the rise of artificial intelligence (AI) in medicine. While opportunities for application of AI and machine learning are emerging across specialties and clinical services, radiology has led in this progress, with AI algorithms used for everything from scanning protocols and pathology detection, to referral systems and workflow optimisation. During the European Congress of Radiology (ECR) 2020, a 'Meets Session' on 'Artificial Intelligence and the Radiographer Profession' provided insights from several expert speakers, discussing the clinical data basis for AI, the ethical and professional considerations for its incorporation into patient care, and the role of radiographers in the AI landscape ahead.

CURRENT UNDERSTANDING

Dr Nicholas Hans Woznitza, Homerton University Hospital, London, UK, gave the opening presentation where he analysed the existing evidence-base, risks, and benefits for the use of AI in radiography and the role ahead for radiographers. He advocated for radiographers to understand AI, its development, and its use in imaging. Discussing the results of a 2019 American Society of Radiologic Technologists (ASRT) survey, Dr Hans Woznitza outlined that the majority of respondents were confident that the AI features of their imaging equipment functioned correctly and provided reliable results, despite having mixed familiarity with the features themselves. To illustrate the need for changes in AI systems to be both evidence-based and clearly articulated to radiographers and imaging healthcare professionals, Dr Hans Woznita pointed to the example of "the Boeing 737 crisis [where] modifications were made to back-end systems that weren't communicated appropriately to pilots with devastating consequences." When considering AI algorithms that determine radiation dose and scan time, the responsibility for delivering that dose of radiation to the patient still falls to the radiographer and radiologist. Confidence in the AI evidence-base and knowledge of the AI system are crucial parts of that responsibility, Dr Hans Woznita emphasised: "We need to be empowered with thorough evidence to inform our decision-making and to make sure our practice isn't compromised."

BENEFITS AND RISKS

Dr Hans Woznitza went on to discuss the benefits and limitations of AI in clinical imaging. The benefits of AI in medical imaging hinge around radiation risk. AI algorithms can help to optimise scanning protocols to minimise scanning time

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and radiation exposure. AI algorithms can also be useful in referral protocols and justification of scan requirement, to help reduce radiation exposure by avoiding unnecessary scanning. Reduction in scanning time has a further benefit of allowing increased patient throughput, allowing for a greater number of patients to access imaging in a timely manner. The use of AI algorithms to identify which scans are most appropriate for immediate reporting or for consideration of escalation, e.g., from chest X-ray to CT scan, can benefit both patient care and reporting radiographers, as Dr Hans Woznitza highlighted study findings that immediate reporting of imaging results reduces error rates and improves time to diagnosis.

Risks associated with the incorporation of AI in imaging practice include concerns of population-based clinical decision-making rather than individual-based care. Dr Hans Woznitza provided the example of using AI algorithms to predict nonattendance at imaging appointments and justify 'double-booking' to optimise workflow efficiency. This population-based strategy overlooks the reasons why patients may not attend appointments, ignoring the responsibility to engage with these patients to provide them with quality care, and risking entrenching inequalities as socioeconomic factors frequently contribute to nonattendance. Dr Hans Woznitza advocated for the evidence-based progress of AI in medical imaging, highlighting the need for radiographers' skills and understanding of AI to progress alongside these algorithms to maintain their responsibility to patients: "Patients are at the centre of what we do; we are hoping to use AI to improve their experience, to minimise discomfort, [and] to optimise the image quality for the patient's perspective."

"Patients are at the centre of what we do; we are hoping to use AI to improve their experience..."

ETHICAL CONSIDERATIONS

Dr Adrian Brady, Mercy University Hospital, Cork, Ireland, gave the second presentation, discussing ethical considerations for the use of AI in imaging. Given the growth of AI in radiology, many organisations have provided guidelines on the ethical use of AI algorithms. Dr Brady noted some commonalities across these guidelines, particularly the principles 'do no harm', respect for human rights and freedoms, transparency and accountability, and maintenance of human-held control and responsibility. A multisociety statement 'Ethics of Artificial Intelligence in Radiology', published in 2019, provides international considerations for the use of AI, but Dr Brady gave an overview of some of the underpinning ethical questions.

Foundational Truth

To initially develop an AI algorithm, Dr Brady explained, requires massive amounts of validated data; however, these data must be accepted as 'truth' for a reliable basis for AI training. Dr Brady spoke of a New York Times article, 'The Tedium of Teaching AI', which described the process of training an AI algorithm to recognise polyps in colonoscopy; the human workforce labelling the images to train the algorithm was revealed as non-medical workers trained over 7 days of video calls. Alternative methods for training AI algorithms involve the use of already validated, real-world patient data, which poses confidentiality concerns. As an example for this, Dr Brady discussed a case from the USA, where a deal with a private healthcare provider gave a technology company access to tens of millions of individual health records, including all identifiable data, for the purposes of developing new health software; this deal was made without patients' or doctors' knowledge or consent.

Data Ownership and Privacy

The ethics of AI and data ownership are more complex in an international context, as different countries place differing degrees of importance on personal rights versus collective social welfare. Dr Brady outlined some of the global differences in data ownership: in the USA, the company performing the imaging holds the ownership of the imaging data but patients have a legal right to a copy of their data, and patient data may be retrospectively used in research without seeking specific consent; while in the European Union (EU), General Data Protection Regulation (GDPR) legislation means that patients have both ownership and control over their personal and sensitive

information (medical and non-medical), and sharing or using the data requires explicit patient consent. Beyond access to data, clarification of use of data is required. The multisociety 'Ethics of Artificial Intelligence in Radiology' statement recommends Data Use Agreements to specifically describe every allowed use of patient data, with requirements for regular updates to reflect new uses of data and a plan for disposal of data once an agreement ends. Among the types of companies seeking access to patient data are companies that also own social media platforms, search engines, or mobile phone technology, which raises ethical concerns as they could potentially target people for advertising or extort patients over release of their medical information.

Data Bias

Data bias impairs the ethical use of AI in imaging. If the dataset used to train an algorithm does not reflect the patient population receiving the imaging using that algorithm, the bias in the foundational data may negatively affect patient care. As a result, Dr Brady believes there is an ethical duty for transparency of the clinical truth of datasets. Understanding the value of the foundational data, and the process by which the algorithm interprets these data for clinical processes, is also important for patient communication. For patients to have confidence in their care, and for clinicians to behave in an ethical manner in providing that care, AI must be well-built and well-understood. Dr Brady said: "A lot of what happens in AI happens in a 'black box' environment, yet we have to build in interpretability (the ability to understand what's going on), explainability (the ability to explain what has happened), and transparency (the ability for a third party to see what's gone on and to understand how a decision was arrived at)." Dr Brady closed his presentation with a quote from Prof Steven Hawking: "Our future is a race between the growing power of our technology and the wisdom with which we use it."

FUTURE DIRECTIONS AND THE ROLE OF RADIOGRAPHERS

The final presentation was provided by Dr Melissa Jackowski, ASRT Past President and Immediate Past Board Chair, Garner, North Carolina, USA, who discussed future applications of AI in radiography. She highlighted the value of AI systems in supporting safety in patient care: "AI could assist the radiologic technologist with dose optimisation by facilitating the building of a personalised protocol for patients and estimating radiation risk relative to cumulative dose and patient age or other parameters." She went on to discuss other specific applications of AI that aim to improve patient safety, including the use of neural networks to train AI systems in mapping ultra-low-dose protocols. Workflow optimisation through the use of AI could help prioritise patients based on level of emergency and appropriateness, to improve both patient safety and health service efficiency. Finally, AI used in the detection of some pathologies, such as pneumothorax on chest X-ray, can escalate imaging results to radiologists more rapidly, reducing delay in diagnosis.

Despite the capabilities of AI and potential benefits for patient safety and health service workflow, there are challenges to its incorporation into clinical practice. Dr Jackowski spoke of the limitations of machine learning, particularly as AI algorithms can only determine decisions once information reaches a 'tipping point' and cannot extrapolate from incomplete data or make judgement calls in the way that humans can. In addition to ethical and data concerns, Dr Jackowski addressed the challenges for medical imaging professions in developing education, training, and workplace task flows that support understanding and application of AI, and are flexible enough to evolve with this rapidly developing field. Disruption to workflow and workforces as education and training requirements shift requires support and education of the existing medical imaging workforce. To facilitate this evolution, Dr Jackowski advocated for radiographers and medical imaging professionals to lead efforts to incorporate these AI systems into clinical use, to champion the focus on quality and safety in patient care, and to encourage ethical guideline conformity across stakeholder groups. She emphasised the opportunity for radiographers and medical imaging professionals to act as "pioneers" in incorporating AI into practice: "become involved in laying the groundwork for ethical, practical, patient safety, and clinical aspects of AI in their responsibilities and for the betterment of patient care."

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Abstract Reviews

In the following abstract summaries, international experts in the field of radiology share insights from their abstracts presented at the European Congress of Radiology (ECR).

CT Imaging Texture Analysis: Evaluation of Variability Sources in the Different Steps of Radiomic Workflow

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Keywords: CT imaging, features variability, radiomic workflow, texture analysis.

Citation: EMJ Radiol. 2020;1[1]:26-28. Abstract Review No. AR1.

BACKGROUND AND AIM

One of the main issues in radiomics is the heterogeneity of data and methods of analysis because each step of a radiomic study hides pitfalls that, in the end, can combine and lead to the failure of the whole process.[1-3] Several works can be found in the literature concerning single sources of variability, but they do not provide conclusions on the whole workflow.[4-6] The aim of this work was to analyse the main sources of textural radiomic features (RF) variability in the different steps of the radiomic workflow,[1] to quantify its extent, and evaluate possible recommendations for its reduction.

MATERIALS AND METHOD

For each step of the radiomic workflow, potential sources of variability concerning CT imaging were analysed (Figure 1).

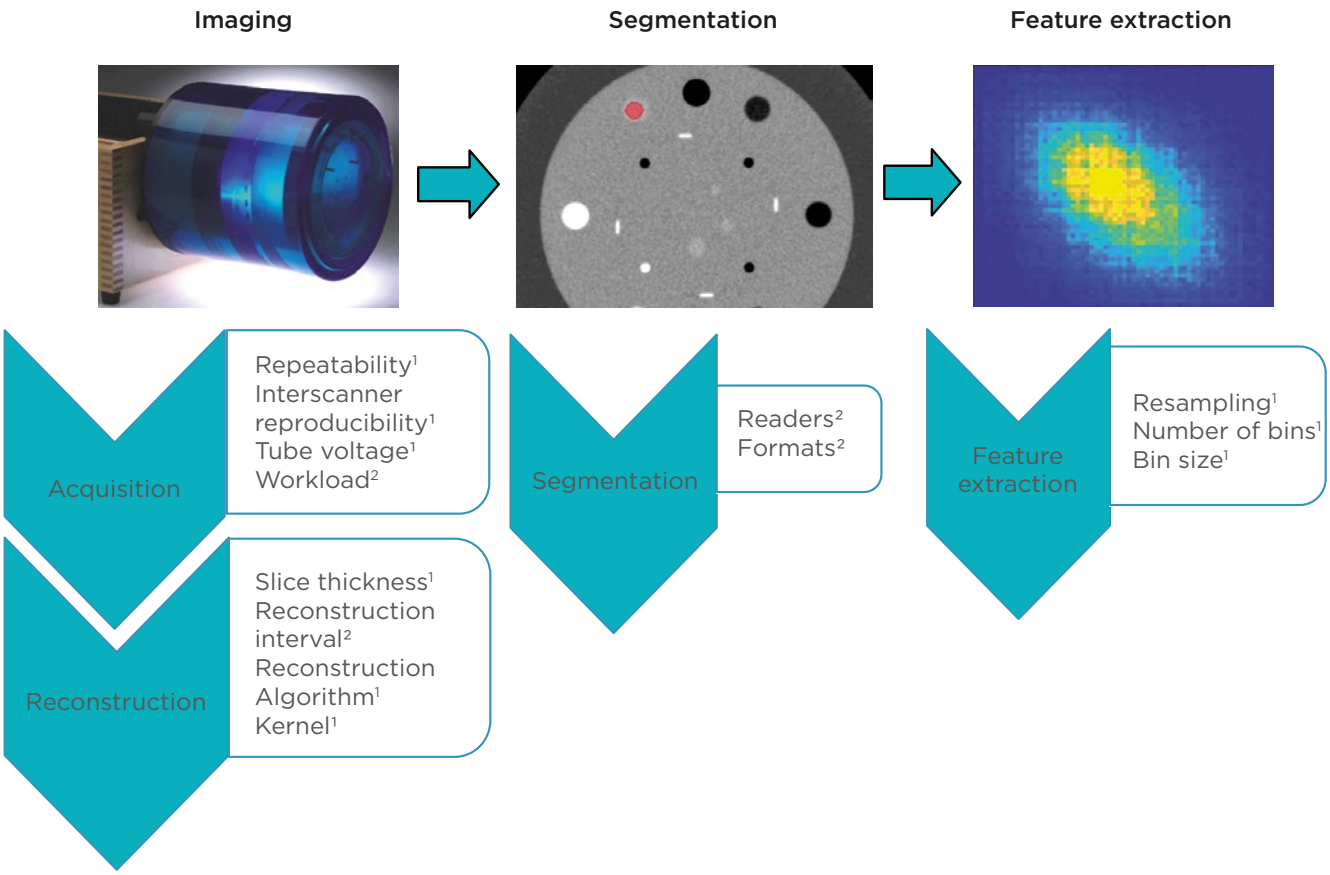

Figure 1: Analysed variability sources within the different steps of the radiomic workflow.

Most of the analyses were performed on phantom acquisitions,[1] while patients' images[2] were used to test some parameters considered not significant on a phantom.

The authors focussed on intrascanner repeatability, interscanner reproducibility, tube voltage, and automated workload in the acquisition step; slice thickness, interval, algorithm, and kernel for the reconstruction step; inter-reader and interformat variability in segmentation; and voxel resampling and parameters for features extraction.

The analyses were performed on Catphan® (The Phantom Laboratory, Salem, New York, USA) acquisitions and patients' images. A wide set of scanner manufacturers and models was considered involving different centres. The software used for segmentation and features extraction were IntelliSpace Portal 8.0 (Philips Medical Systems, Amsterdam, the Netherlands), 3DSlicer,[7] and IBEX.[8]

The effect of the different sources of variability on RF was expressed in terms of relative standard deviation (RSD) or relative discrepancy.

RESULTS

In the imaging acquisition step, intrascanner repeatability, interscanner reproducibility, and tube voltage caused high RF variability, with RSD ranging from 0% to 800% and a mean value of 30%. On the other hand, the automated workload was demonstrated to not strongly affect RF values.

Regarding imaging reconstruction, the most crucial parameters were algorithm and kernel with RF variations, in terms of relative discrepancy and RSD, up to 600% and 400% and mean values of 50% and 20%, respectively.

The inter-reader variation in contouring was overall the largest source of variability, with mean and maximum values of 60% and 1,000%, respectively.

In the RF extraction step, the interslice resampling appeared not a useful solution, while the choice of the feature category

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parameters was the most critical point to standardise in the radiomic workflow. In addition, changes in these values unpredictably affect the variabilities caused by the other parameters.

Overall, seven textural RF (out of 32) showed a variability within the 10% for all the analysed issues, and 19 RF did not exceed the 20% either way.

CONCLUSION

A phantom study is preparatory to determine an optimal workflow that maximises RF predictivity on patients. Some variability sources can be limited or removed through standardisation processes, especially for the imaging reconstruction and RF extraction steps. Nevertheless, the issues due to acquisition and inter-reader variability remain. Regarding the acquisition step, the main effect on RF stability is attributable to reproducibility, which at present is unavoidable in multicentric studies. On the other hand, inter-reader variability might be limited through automatic segmentation tools. Finally, variability sources and the different behaviour of RF must be evaluated depending on the trial characteristics in order to find a compromise between stability and predictivity.

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The Incidence of Penetrating Aortic Ulcer as a Cause for Non-Aneurysmal Rupture of the Abdominal Aorta

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Keywords: Acute aortic syndrome, aortic aneurysm, aortic emergencies, penetrating aortic ulcer (PAU).

Citation: EMJ Radiol. 2020;1[1]:28-30 Abstract Review No. AR2.

BACKGROUND AND AIM

Penetrating aortic ulcer (PAU) is a typical manifestation of thoracic acute aortic syndrome.[1] Nevertheless, selected reports also notify the presentation of PAU in abdominal aorta.[2] Moreover, some would say that it is a main cause of spontaneous rupture of non-aneurysmal, non-infected abdominal aortas.[1,3] PAU is defined as an atherosclerotic lesion of the aortic wall with ulceration of intimal and medial layers and rupture of the internal elastic lamina. The lesion typically affects elderly patients with systemic atherosclerosis.

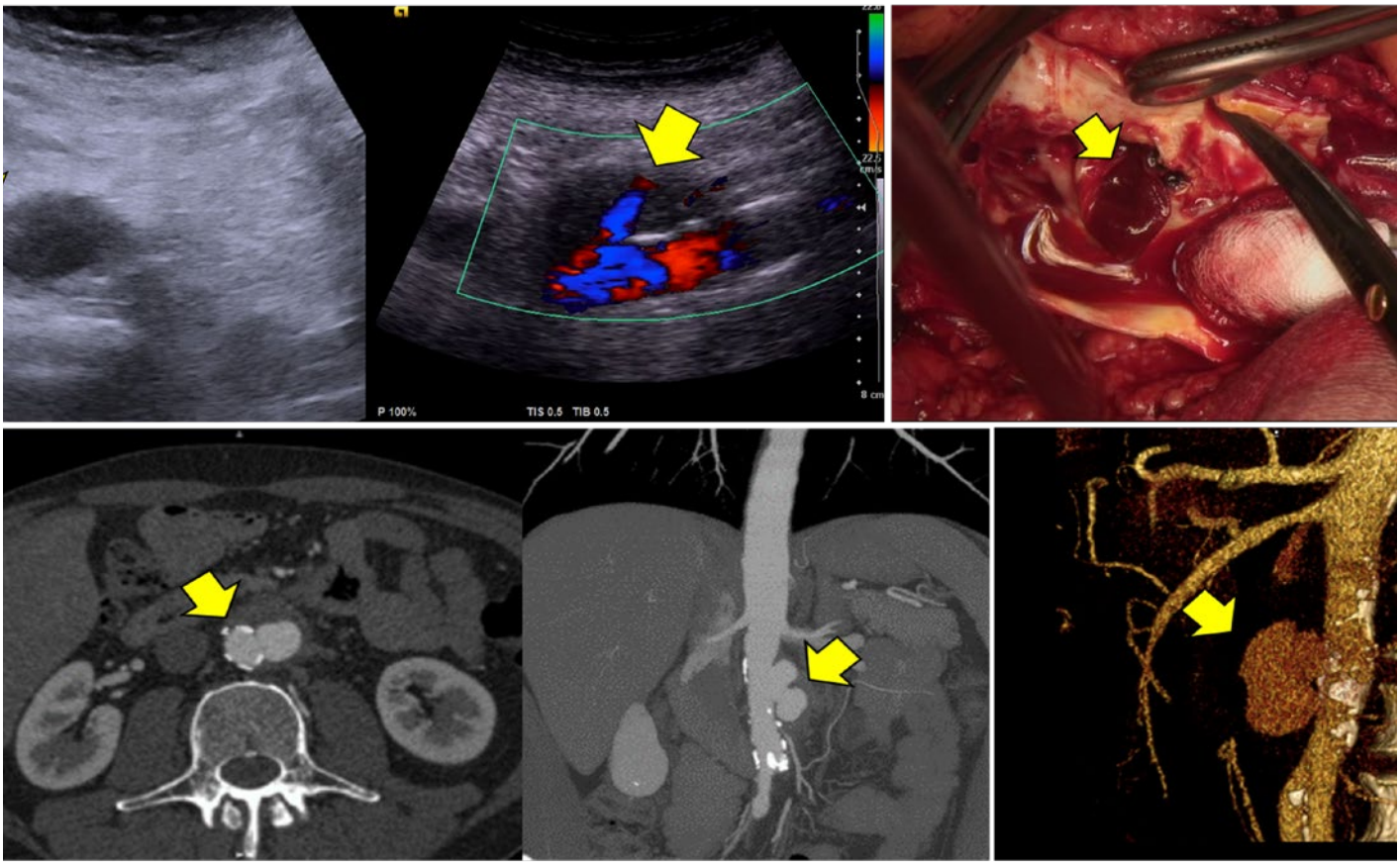

Figure 1: The presentation of PAU-related rupture of abdominal aorta on ultrasonography (above left and middle), on CTA (below) and intraoperatively (above right). The arrow marks an extravasation via ulceration.

Due to the comparative rarity of PAU in the abdominal aorta, only single reports regarding single cases are available.[4] In this study, the authors analysed their experience of the diagnosis and management of complicated PAU in abdominal aorta.

MATERIALS AND METHODS

Over the last 15 years, the authors observed 48 patients (median age: 61 years; female: n=33) with complete rupture of non-aneurysmal abdominal aorta as a result of PAU. All patients were symptomatic and reported abdominal and/or back pain and of clinical signs of internal bleeding. Thus, aneurysmal rupture was the prime suspicion on admission. The diagnosis was determined by ultrasound and CT angiography.

RESULTS

The radiological findings included typical signs of PAU (the same as signs seen in thoracic aorta) presenting as non-dilatated aorta with strong calcification of the wall, single or multiple crateriform ulcers, and ulcer bottom defect with extravasation (Figure 1). In this area, retroperitoneal haematoma with contrast uptake was detected. In rare cases, if the PAU, and consequently the rupture, is located in the posterior wall of aorta, a temporary restricted (two-stage) rupture without signs of continuing bleeding can be observed. The following histopathological examination confirmed PAU with wall destruction. The majority of patients underwent surgical repair (35 open and nine endovascular). Seven patients died.

CONCLUSION

The authors' experience indicates that PAU in abdominal aorta and its following non-aneurysmal rupture is relatively rare, but not the cause of aortic emergency conditions. This should be suspected in each case of non-traumatic retroperitoneal bleeding.

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The diagnostical and tactical approach should be the same as taken in cases of thoracic acute aortic syndrome.

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Intrinsic and Extrinsic Academic Motivation in Radiography Students

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Keywords: Academic motivation, education and training, educational outcomes, radiographers, radiography.

Citation: EMJ Radiol. 2020;1[1]:30-32. Abstract Review No. AR3.

BACKGROUND AND AIM

Patient well-being has always been a guiding value in the conduct of radiographers, which is currently a measurable requirement, incorporated into a fundamental concept: the provided quality of care. Thus, in this context, universities have an increased responsibility in preparing future radiographers so that they can respond to the patient's needs. This training is a process under constant development, in which the necessary conditions for radiography student participation must be provided. The main purpose of the present research was to investigate academic intrinsic and extrinsic motivation, and amotivation as a function of age and gender in radiography students across the country.

METHOD

A paper-based survey was used, based on an original French scale (*Echelle de Motivation en Education*), later translated into English by the authors Vallerand et al.[1] This scale consists of 28 items subdivided into seven subscales, scored on a Likert scale of 1 ("strongly disagree") to 7 ("strongly agree"). This seven-factor uncorrelated measurement model allowed the assessment of: a) the intrinsic motivation for learning, for accomplishment, and for stimulating experiences; b) external regulation, introjected regulation, and identified regulation (extrinsic motivation); and c) amotivation.[2-4] A final sample of 314 radiography students was obtained, 78.3% of radiography students were from public universities.

RESULTS

Exploratory factor analysis with the extraction of the factors through the principal component analysis using varimax rotation was performed and four new factors/dimensions were obtained (Table 1).[5]

Table 1: Total variance explained.

Component	Initial eigenvalues			Extraction sums of squared loadings		
	Total	% of variance	Cumulative %	Total	% of variance	Cumulative %
1	4.568	32.627	32.627	4.568	32.627	32.627
2	2.167	15.481	48.108	2.167	15.481	48.108
3	1.607	11.482	59.590	1.607	11.482	59.590
4	1.185	8.465	68.055	1.185	8.465	68.055
5	0.817	5.836	73.891			
6	0.620	4.425	78.316			
7	0.560	4.002	82.318			

Extraction method: principal component analysis; SPSS output.

Factor 1 explained 32.6% of the total explained variance and the remaining three factors explained 15.5%, 11.5%, and 8.5%, respectively.[5] Together they explained approximately 68% of the total variability. Acceptable values of internal consistency were obtained for the items of the various dimensions, since Cronbach's alpha values were between 0.851 for the identified regulation and 0.745 for the introject regulation.[3,5-7] There were statistically significant differences in motivation between female and male students ($p<0.05$);[1,8] it was also found that age, gender, type of education, and curriculum year influence the academic motivation of radiography students.[1-3,7,8] The self-determined motivation (SDF) index was also evaluated, and was found to be statistically correlated with all the motivation subscales.[1] It was observed that learning is the subscale most strongly and directly correlated with the SDF (rho: 0.565; p=0.000) and the introject regulation is the least correlated (rho: 0.206; p=0.000). In fact, there is a moderate and direct relationship between the SDF and all subscales (motivation rho: 0.521; p=0.000, identified regulation rho: 0.371; p=0.000).[1,3,8]

CONCLUSION

The present research has allowed the authors to map the dimensions of motivation that characterise the undergraduate radiography course. The motivation of the radiography students could be described by four dimensions: learning process, identified regulation, introjected regulation, and amotivation. In general, radiography students have high levels of intrinsic and extrinsic motivation and low levels of amotivation. These signs may suggest that these radiography students have good academic performance and a self-determined behaviour.[2,8] Further research is required; however, the authors consider it essential for universities to develop and delineate strategies during training that encourage a motivated behaviour from radiography students.

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Optimisation of a Native Cardiac Scan Protocol in the Post-Mortem CT

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Keywords: CT, post-mortem, post-mortem CT, prospective study, protocol optimisation.

Citation: EMJ Radiol. 2020;1[1]:32-33. Abstract Review No. AR4.

BACKGROUND AND AIM

CT has become an established practise in forensic imaging, in which this method is called post-mortem CT. In contrast to clinics, to date only a small number of published scientific publications on protocol optimisation exist. Because the accuracy of radiological image data evaluation is dependant on the image quality, these studies are essential. Furthermore, compared to the examinations of living patients, motion artifacts and radiation dose do not have to be considered in the post-mortem field.[1-8]

The aim of this study was to evaluate the current institute standard of the Institute of Legal Medicine for a native cardiac post-mortem CT at the University Medical Center Hamburg-Eppendorf, Hamburg, Germany, in regard to image quality and whether or not optimisation of this protocol was achievable.

METHODS

For this purpose, a prospective study with five bodies was carried out in January 2019. The cadavers were scanned with five different heart protocols, which is the institute standard, and four protocols were developed for this study. The protocols deviated from each other in the scan parameters kVp, mAs, slice thickness, and increment (Table 1). Scan range was from the middle of the larynx to the phrenicocostal sinus. Each cadaver was stored in supine position, the arms were tied together using medical tape and were positioned over the head.

The protocols were assessed by a 5-point ordinal-LIKERT-scale questionnaire from four independent radiologists, without knowledge of the institute standard. Using Microsoft Excel and SPSS Statistics, the questionnaires were evaluated and then inter-rater reliability (Kendall´s coefficient of concordance) was calculated in order to evaluate the agreement between the assessors.

RESULTS

The results show that the higher slice thickness protocol was rated higher in terms of image quality than any other protocol. Likewise, the two higher-dose protocols also performed better than the institute standard. The lower-dose protocol was rated as the worst. After calculation of the inter-rater reliability, an acceptable agreement between the raters could be assumed.

Table 1: Overview of all five cardiac scan protocols.

	Protocol A (Institute standard)	Protocol B	Protocol C	Protocol D	Protocol E
kVp	120	120	120	120	140
mAs	250	350	180	250	250
Slice thickness	0.8	0.8	0.8	1.5	0.8
Slice increment	0.40	0.40	0.40	0.85	0.40

Protocol A is the institute standard, the other four protocols were created for this study.

DISCUSSION

Despite the clear results, there are some limitations regarding this study; only a small number of cadavers were included and only adult cadavers were studied. In order to ensure a practical environment, the protocols must also be examined in children, infants, and adolescents. Furthermore, the protocols in the image data received by the raters were labelled and arranged in the same way in all cases, which is why a bias of the assessors cannot be ruled out. Additionally, the results did not allow for any evaluation of the protocols' diagnostic value. For this, further studies are necessary. Future research should also clarify the question of whether a combination of a higher slice thickness with a higher dose can lead to a more enhanced image quality.

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Mental Health and Wellness Education for Medical Radiation Technologists: Workplace Implications and Attitudes

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Keywords: Continuing professional development, education, experiential learning, mental health, medical radiation technologists (MRT), professional issues, storytelling, radiographers, workforce.

Citation: EMJ Radiol. 2020;1[1]:34-35. Abstract Review No. AR5.

BACKGROUND

The Mental Health Commission of Canada reports healthcare workers are 1.5 times more likely to be absent from work than other sectors, with mental illness being the leading cause of disability.[1-3] Today's healthcare worker faces many occupational hazards, including, but not limited to, shift-work and workplace violence. Furthermore, staying current in a rapidly changing practice environment adds additional stress.[3] A Canadian survey examining mental health of medical radiation technologists (MRT) found 57.0% feel moderate to high levels of emotional exhaustion at work, 15.0% reported high levels of depersonalisation, and 55.4% reported having too much work to be able to complete it to a satisfactory standard.[4]

MRT engage with patients from diagnosis through to treatment, providing care in a variety of circumstances including trauma cases, emergency, and operating rooms; providing daily oncology treatments; imaging patients with chronic illnesses over multiple years; and providing forensic imaging. MRT bear the burden of knowledge, often being the first to witness a pathology or condition, while maintaining a caring and compassionate, yet professional, composure with patients. These circumstances shape MRT practitioners, contributing to the emotional burden experienced.

METHODS

Recently, professional development for MRT has focussed on technological advancements like artificial intelligence, deep learning, or hybrid imaging. Recognising the need for mental health education, the Atlantic MRT Accord piloted a full-day conference with the aim of addressing the gap in mental health learning opportunities. Sessions on organisational change, post-traumatic stress disorder, burnout, vicarious trauma, compassion fatigue, and self-care were provided. A technologist story telling panel and mindfulness-based stress reduction session provided opportunity for deeper engagement. A post-conference survey assessed changes in attitudes and beliefs consequential to the conference. They survey assessed perceptions about mental health leave, stigma, and possible changes in perception of one's own mental health or that of colleagues.

RESULTS

MRT who report regularly considering the mental health of their colleagues increased by 17% following the conference. The number of respondents reporting being somewhat to very familiar with mental health concepts increased by 15%. Additionally, 95.0% of respondents reported designated mental health days were important for best work performance; however, only 13.9% of respondents reported satisfaction with availability of support to take them. This coincides with national data, indicating 56.4% of MRT do not have, or are unsure of, stress management support at work.[4] Furthermore, 90% of respondents indicated reporting to work in spite of needing to take a

mental health day. Further showing the effect stigma has in the MRT community, 37% of respondents recall reporting unrelated physical symptoms when requiring a mental health day as a means of justification. While many Canadian healthcare organisations have signed a declaration of commitment to psychological health and safety in healthcare, protected mental health days are not the current practice. This evidence suggests that stigma is active within the MRT community, preventing MRT from taking the time needed to deal with, and heal from, the emotional burden that comes with this profession.

CONCLUSION

Future research aimed at providing broader perspective on the mental health of MRT and the impact of work-related stressors on their practice and wellbeing is warranted. Such information is essential to the development of programmes that support self-care. These actions will shape the evolution of compassionate practice, not only for patients, but for healthcare practitioners themselves and towards their colleagues.

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^{18}F-FET or ^{18}F-FCH PET/CT in the Primary Diagnosis of Low-Grade Glioma: A Pilot Study

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Keywords: Fluoromethyl-(18F)-dimethyl-2-hydroxyethyl-ammonium chloride (FCH), O-(2-[18F]-fluoroethyl)-L-tyrosine (FET), low-grade glioma (LGG), PET/CT.

Citation: EMJ Radiol. 2020;1[1]:35-37. Abstract Review No. AR6.

BACKGROUND AND AIM

Gliomas are associated with variable survival, linked to their histological type.[1] Although traditionally gliomas behave as if benign, low-grade gliomas (LGG) gradually evolve into high-grade tumours. Within 5 years, this will occur in approximately one-half of patients.[2] The diagnosis of LGG is challenging because conventional imaging modalities can often give inconclusive or equivocal results.[3]

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Table 1: Diagnostic workout of patients included in the study.

Patient number	FCH PET	FCH SUV max	FET PET	FET SUV max	Histology	Grade	IDH status
1	negative	0.0	positive	1.7	diffuse astrocytoma	II	NOS
2	negative	0.0	negative	0.0	NA	NA	NA
3	negative	0.0	positive	2.0	diffuse astrocytoma	II	mutant
4	positive	1.6	positive	3.0	glioblastoma	IV	mutant
5	negative	0.0	positive	2.8	diffuse astrocytoma	II	mutant
6	positive	3.9	positive	3.1	glioblastoma	IV	NOS
7	negative	0.0	positive	1.8	ganglioglioma	I	NA
8	negative	0.0	positive	1.5	diffuse astrocytoma	II	mutant
9	negative	0.0	negative	0.0	NA	NA	NA
10	negative	0.0	positive	1.3	anaplastic astrocytoma	III	mutant
11	negative	0.0	positive	1.7	ganglioglioma	I	NA

FCH: Fluoromethyl-(18F)-dimethyl-2-hydroxyethyl-ammonium chloride; FET: O- (2-[18F]-fluoroethyl) -L-tyrosine; IDH: isocitrate dehydrogenase; NA: not applicable; NOS: not otherwise specified; SUV max: maximum standard uptake value.

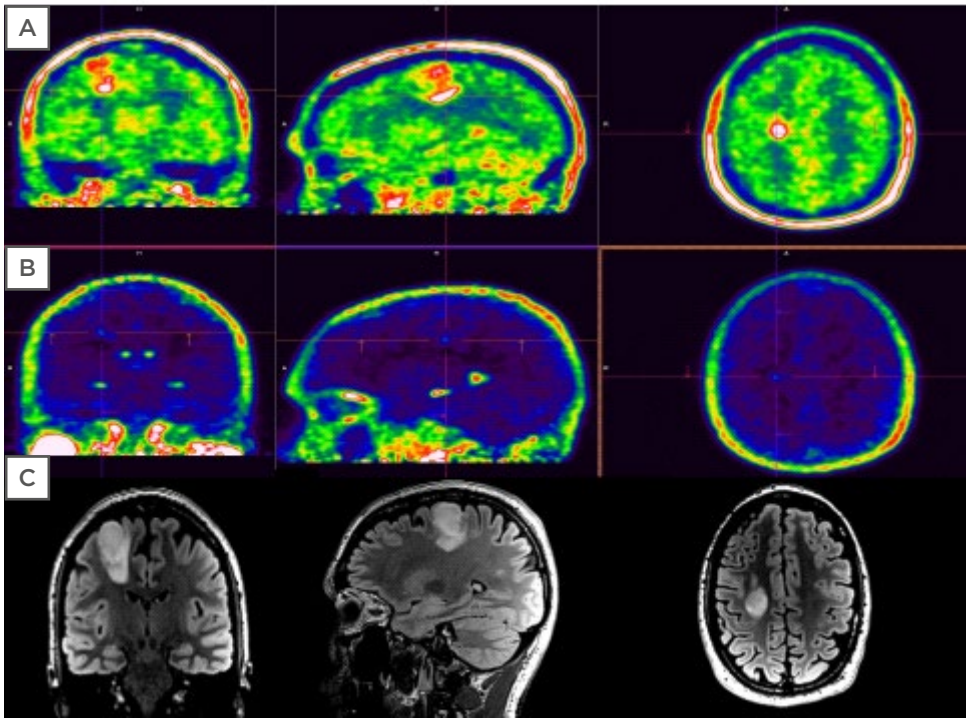

Figure 1: 38-year-old male patient with World Health Organization (WHO) Grade II diffuse astrocytoma.
A) positive ^{18}F-FET PET/CT (SUV max: 2.8); B) negative ^{18}F-FCH PET/CT; and C) MRI of a fast fluid-attenuated inversion recover tumour in right frontal lobe.

FCH: Fluoromethyl-(18F)-dimethyl-2-hydroxyethyl-ammonium chloride; FET: O-(2-[18F]-fluoroethyl)-L-tyrosine; SUV max: maximum standard uptake value.

Functional imaging modalities can provide additional metabolic information in the management of patients with LGG. O-(2 [18F]-fluoroethyl) -L-tyrosine (^{18}F-FET) is a radiopharmaceutical approved for the characterisation of glioma-suggestive brain lesions.[4-6]

^{18}F-FET displays a high tumour-to-background ratio and no accumulation in inflammatory lesions. Because of low uptake in normal brain parenchyma, some centres use fluoromethyl-(18F)-dimethyl-2-hydroxyethyl-ammonium chloride (^{18}F-FCH) PET for the characterisation of glioma-suspected brain lesions. The aim of this study was to determine the diagnostic accuracy of ^{18}F-FET and ^{18}F-FCH PET/CT in patients with primary LGG.

METHODS

11 patients aged 21–80 years with MRI-suspected LGG were involved. Patients underwent both ^{18}F-FET and ^{18}F-FCH PET/CT within 1 week. Brain PET/CT was performed according to standard protocol: 20 min after intravenous injection of 185MBq of ^{18}F-FET and 185MBq of ^{18}F-FCH PET. Surgery and histological diagnoses were performed in the following 2 weeks.

All 11 patients with suspected LGG underwent MRI, ^{18}F-FET, and ^{18}F-FCH PET/CT. All patients had LGG according to MRI. In all PET-positive patients, tumour location on MRI was consistent with region of PET/CT positivity. Two out of 11 patients included in this study did not undergo surgery or biopsy for histological confirmation. Both had negative ^{18}F-FET PET and negative ^{18}F-FCH PET scan, so they declined surgery and multidisciplinary tumour board recommended follow-up. Nine out of 11 patients with suspected LGG had final histological diagnosis after the surgery.

RESULTS

The results of the study are summarised in Table 1. Significantly better concordance was described between tumour histology and ^{18}F-FET PET results (weighted κ: 0.74) compared to both ^{18}F-FCH (weighted κ: 0.15) and MRI results (weighted κ: 0.00). Significant association between tumour histology and ^{18}F-FET results was found (odds ratio: 12.87; 95% confidence interval [CI]: 0.49–333.70; p=0.013, logistic regression analysis). Most patients with histologically-proven LGG had negative ^{18}F-FCH and positive ^{18}F-FET (Figure 1).

CONCLUSION

These results demonstrate that the appropriate radiopharmaceutical should be chosen before performing PET/CT scan in patients with newly diagnosed LGG. The ^{18}F-FET PET/CT is more accurate than ^{18}F-FCH to detect LGG.

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Congress Interview

On the following pages are interviews with key members of the European Society of Radiology (ESR), in which they discuss their roles within society and current topics in radiology.

Dr Adrian Brady

Mercy University Hospital, Cork, Ireland
Previous Chair of the European Society of Radiology (ESR) Quality, Safety & Standards (QSS) Committee, ESR 2nd Vice-President

Q1 Up until March 2020, you were the chair of the ESR QSS Committee. Could you tell us what your main duties were in this role and the committee's mission?

I had the honour of chairing the QSS Committee from March 2017, and my 3-year term came to an end in March 2020, after which I was replaced by Dr Núria Bargalló Alabart, and became the ESR 2nd Vice-President.

As QSS Committee Chair, I sat on a number of subcommittees, and acted as a liaison between them and the ESR Executive Council. I co-ordinated the activities of these groups, where they intersect or overlap with one another, and worked to ensure that the overall goals of the ESR were pursued in an integrated manner by all the different subcommittees and working groups that come under the umbrella of the QSS Committee. I also represented the different arms of the QSS element of the ESR in other committees, again with the aim of ensuring that all our work was integrated and coherent.

As a member of the Executive Council (and now also of the Board of Directors), I participate in deliberation and decision-making about major activities and initiatives across all the breadth of ESR activity, in conjunction with other members of the Board of Directors and other committee chairs and Executive Council members.

The remit of the QSS Committee is to guide the Society in issues that relate to quality of radiology service, patient and staff safety, and standards for performance of our work. This is a very wide range of areas, encompassing activities such as radiation protection, clinical decision support, audit, eHealth and informatics, and much more.

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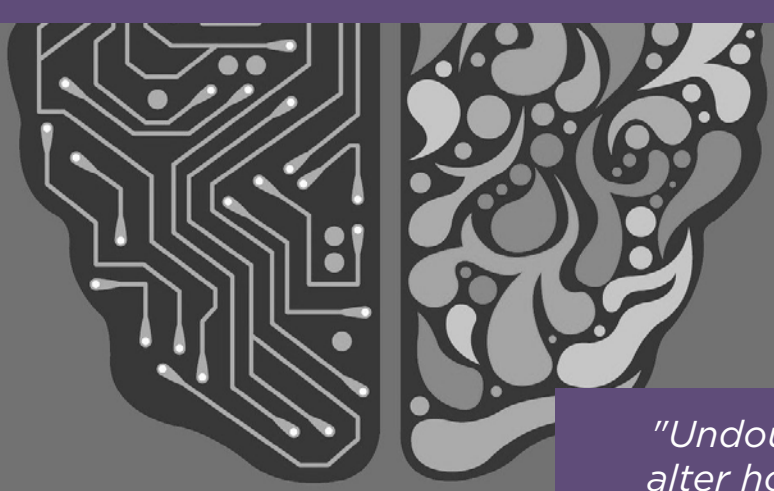

"Undoubtedly, AI will alter how we practise radiology"

Q2 Could you share with us some of the projects that the QSS Committee or associated subcommittees are currently working on, and the impacts that you hope they have?

Our Ultrasound Subcommittee has recently completed a major position paper for the society on performance of ultrasound, which aims to set out the standards under which ultrasound studies should be performed, and the level of knowledge and expertise that should be available to those performing ultrasound.

During ECR 2019, our Audit Subcommittee published version 2 of Esperanto, a guide to clinical audit and a tool to facilitate audit performance. The ESR, in conjunction with the European Society for Radiotherapy and Oncology (ESTRO) and European Association of Nuclear Medicine (EANM), is currently engaged in a 30-month European Commission project (QuADRANT) to establish the status of clinical audit in all European Union (EU) member countries.

The Radiation Protection Subcommittee and the ESR Eurosafe Imaging Initiative are working on different aspects of justification of radiological exposures, taking into account the new requirements under the EU Basic Safety Standards Directive (BSSD).

In 2019, the eHealth & Informatics Subcommittee participated in the writing and publication of a major multi-society statement on the ethics of artificial intelligence (AI) in radiology,[1] and is currently working on a paper on Blockchain technology in radiology AI.

The Referral Guidelines Subcommittee is continually engaged in validation and updating of our imaging guidelines, and in promotion of the ESR iGuide.

All of these projects, and the many others that are also underway, are designed to provide our members with information, standards, and supports, to help them meet legislative requirements, provide the highest-quality care possible, and understand new developments in our specialty. We liaise with many other professional and official bodies across our member countries, in efforts to promote safe, high-quality radiology practice.

Q3 As the Co-chair of the ESR/EFRS Working Group on Patient Safety and an experienced radiologist, how can radiologists protect patients and themselves from unnecessary exposure to radiation?

Radiation protection is fundamental to the education and daily practice of radiologists and radiographers, and is deeply imbued in all we do, from the beginning of our professional lives. Careful legislative control of radiation safety has been strengthened within the EU as a result of the recent translation into national law in all member countries of the BSSD. In our daily working lives, we all strive to ensure that patient exposure to radiation is kept to the minimum necessary to achieve healthcare benefit without risk, and to protect staff from exposure wherever possible. The recently published joint ESR/EFRS paper on patient safety[2] dealt with radiation safety, but also with many other aspects of patient safety, some not quite as obvious.

One very important aspect of radiation safety for patients is justification; legally and morally, any exposure to ionising radiation should

be clinically justified, and radiologists and radiographers have important roles in ensuring that this principle is upheld. The use of decision-support tools (such as the ESR iGuide) in guiding referrers to appropriate use of imaging investigations is a key means of educating those who refer patients for radiological investigation to use radiology services wisely and safely.

Q4 Interest in AI is very prominent in the field of radiology, and is a focus of this year's ESR Congress. How do you see the technology fitting into radiology, and what measures will be put in place to ensure that quality is upheld?

Undoubtedly, AI will alter how we practise radiology. Many fear that it may replace or displace human radiologists, but I believe that this fear is unwarranted. AI tools will automate many of the tasks we perform, and will guide us to new, beneficial outcomes from imaging (e.g., the use of radiomics for personalised prognostication) which are beyond our current visual-based skills. Radiologist time saved from tedious tasks (such as searching for lung nodules) can be deployed in enhanced consultation with referrers and directly with patients. If used wisely, AI tools have the potential to simultaneously benefit patients and increase the ability of radiologists to contribute positively to healthcare for the good of all. As with all new developments in medicine, rigorous post-implementation monitoring of AI products used in radiology will be required to ensure their safety and value; radiologists must be the arbiters of monitoring and maintaining this quality control.

Q5 You have spoken about ethics in AI in radiology and were involved in the joint statement from numerous renowned radiological associations. Are there any key concerns with regard to ethics for the use of AI in radiology, and if so, how can these be addressed?

AI is really all about data; where data come from, how they are used and manipulated, and what can be done with them. Algorithms are mathematical functions, and are intrinsically amoral; they will perform the functions they were designed to perform with no regard for the ethics behind the outcomes unless we, the humans who develop and implement them, build in ethical controls. There are significant ethical issues underpinning the use of patient data for development of radiology AI algorithms, and their use in practice. As we develop the science of AI in radiology, we must concurrently develop and implement ethical codes under which AI is utilised. These complex issues and potential solutions are discussed in the multi-society paper on ethics of AI in radiology published in October 2019.[1]

Q6 Throughout your career you have worked in and with institutions worldwide. Are there any significant differences in radiological practice and safety measures between the countries that you have experienced?

I received my medical and radiology training in Ireland, with further radiology fellowship training in Canada. I've been privileged to work as a radiologist in Ireland, Canada, and (very briefly) the UK, and to teach and lecture in many other countries. While there are differences in how medical care is organised and delivered among all countries, the fundamentals are universal. There is a thirst for and openness to radiology education everywhere, and a sincere desire to deliver the highest-possible quality of care with the available resources.

No country's healthcare system is perfect. In an ideal world, I would like to see a system that delivers appropriate care in a timely fashion, in an affordable way, and without bias or discrimination, according to need.

One feature of some systems which I've observed is a sclerotic approach to new developments, which can lead to resource availability lagging years behind technical capability and clinical innovation. If increased access to diagnostics, especially radiology, confers proven benefit, then the radiologist and other staff numbers needed to deliver those services and the equipment they need to do their jobs must be provided. False economies of restricting resources to limit utilisation lead to worse outcomes in the long term, often at greater ultimate expense.

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I'm very glad to be able to say that awareness of safety issues and the need for radiation protection is a very prominent part of radiologists' lives everywhere The growth of initiatives such as Eurosafe Imaging (and other similar initiatives in other parts of the world) has been really helpful in establishing principles of safe practice and promoting education about safety.

Q7 You have published and spoken about potential errors in radiology. Are there any simple steps that radiologists and their department can take to reduce the occurrence of errors or discrepancies?

Humanity is inherently imperfect, and this also applies to our work, however we might wish it were otherwise. There is no magic formula to achieve perfect, reproducible accuracy in all radiology practice (or, indeed, in any other branch of medicine, or in life in general). The recognition of this does not, however, absolve radiologists of the imperative to take all steps available to minimise error. These steps begin with the recognition that error occurs. From this follows the need to educate ourselves about the reasons for error, and the common pitfalls into which we can fall. An open acknowledgement of the potential for error, and a willingness to learn from it come next, including structures for non-judgemental sharing of learning about mistakes and pitfalls (e.g., meetings in which we learn collectively from cases where errors have occurred). These steps can only be achieved if any fear of litigation or judgement is removed from the process; the threat of sanction for making a mistake works against the principle of learning openly from that mistake.

Q8 Are there any current challenges in radiology, and how they can be potentially overcome?

Life is full of challenges; isn't that what makes it enjoyable? Since its beginning as a specialty, radiology has been subject to innovation and change, often at a rate much faster than most other specialties. New techniques and modalities have changed the way we do things, and the things we do, with every passing generation.

AI, machine learning, and radiomics may prove to be one of the most influential generation-defining changes in the current era. All radiology practice will, in time, be influenced by these tools, and they may fundamentally change the role of the radiologist. It's incumbent on educators to prepare future colleagues for the world of algorithm-assisted radiology, and to ensure that radiology remains a human-led, empathic, and patient-centred specialty.

Our success as a specialty has led to another major challenge: the expectation that we can and should deliver increasing volumes of imaging at increasing speed. We must guard against becoming no more than a commodity, a virtual machine from which results are delivered after inputs of questions. Our centrality in patient care must be reflected by our willingness to deal directly with both referrers and patients. We must support critical thinking in determining what radiology usage is appropriate; clinical decision support tool use should become an automatic element of accessing our services.

Q9 The field of radiology is known for its rapid progression. What do you think the future holds for radiology?

This is perhaps the most difficult question asked here. The short answer is: 'Change'. But if the same question had been asked at any period over the 125 years of radiology practice, the same answer could have been given. As I've said above, ours is a specialty that has continually revised and re-invented itself, as we have adapted to and exploited new developments. It's easy to say we will change in the future, but much harder to identify what form that change will take. What I can say with certainty is that radiologists of the future will embrace whatever new developments come along, put them to good use, and learn ways to make them work for the benefit of patients. It's what we do.

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Prof Valérie Vilgrain

Chair of Radiology Department at Beaujon University Hospital, Clichy, France
Professor of Radiology at University of Paris, Paris, France
Director of the European School of Radiology (ESOR) for the European Society of Radiology (ESR)

Q1 From the early stages of your career you have chosen to specialise in radiology, especially abdominal imaging. What is it about this specialty that interests you?

Actually I started a residency programme in internal medicine and neurology. Working with radiologists, I realised that the radiological specialty was most interesting, being in the middle of the diagnosis and often the treatment. Then I changed to a radiology residency.

In the late 1980s in France, there was already a trend to organ-based subspecialise. I chose abdominal radiology because it is a huge field with many issues: emergency, oncology, and interventional radiology. Since that time I am most happy working very closely with hepatologists, gastroenterologists, surgeons, and pathologists.

Q2 You have authored >450 research articles; which of these publications do you believe have had the biggest impact on radiology healthcare?

As a radiologist, there are not many articles that deeply change patient management. We mostly contribute by showing improvements in diagnostic or interventional procedures but few have massive impact on patient healthcare. I think my most important publication is related to the SARAH trial that compared the reference treatment (sorafenib) to interventional procedure (radioembolisation) in advanced hepatocellular carcinoma, published in 2017.[1] We showed no difference in overall survival but radioembolisation was better tolerated and had fewer adverse events.

Q3 In addition to your extensive research contributions, you have been a reviewer for many prominent journals, are an associate editor, have spoken at many international conferences, and are a member of several international societies. What do you consider to be your greatest achievement?

Having been invited to give honorary lectures at ECR, European Society of Gastrointestinal and Abdominal Radiology (ESGAR), and other international meetings were indeed great achievements. Besides, I still enjoy and learn a lot to serve as a reviewer or associate Editor in prominent journals.

Q4 As the Director of the ESOR, could you explain what its goals are for the field of radiology?

In radiology, as in the other medical specialties, education is key. The three main goals of ESOR, set at its inception in 2005, are still to assist in harmonising radiological education throughout Europe, by supporting the adoption and utilisation of the European Training Curricula; to build a genuine and firm interest in subspecialisation in radiology; and to raise the scientific profile in radiological education in Europe and around the globe.

Q5 Could you tell us about any exciting projects that are currently being organised by ESOR?

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Briefly, ESOR delivers courses with a high level of interactivity combining lectures and workshops. There are different formats but the spirit is to bring education to those who need it. Two-thirds of the courses are in Europe and one-third are international in Asia and Central and Latin America.

"ESOR has a wide programme of scholarships and fellowships to give a unique opportunity to young radiologists, last year residents, or young fellows"

Besides the courses, ESOR has a wide programme of scholarships and fellowships to give a unique opportunity to young radiologists, last year residents, or young fellows to have an in-depth experience in another academic centre. These programmes are open to European and non-European radiologists.

Q6 The slogan for ECR 2020 was 'A Clear Vision for Radiology.' What does the ESR hope that the key take-home message from the congress were?

Our medical specialty, like others, might significantly change in the future. We should, as the largest radiological Society in the world, envision the future and prepare the new generations to be major players in medicine. Indeed, education is the driving force.

Q7 An overarching theme of ECR 2020 was artificial intelligence. Over the years that you have been practising as a radiologist, how have you seen the field change in terms of advancements to the technology of medical imaging?

In our clinical practice, changes are limited nowadays. Yet the active research will certainly bring breakthroughs in the near future in many ways such as workflow, examination acquisition, and patient pathway.

Q8 What are your aspirations for the future of radiology, and what is the most important lesson you have learnt so far in your career?

Radiology is often seen as a technical medical specialty and indeed it has changed fast these last decades. In the meantime, as radiologists we are more and more involved in the patient pathway being major stakeholders during tumour boards. My aspirations are to continue in these two directions and to remain patient-centred.

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Prof Nandita deSouza

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Q1 As the Chairperson of the European Imaging Biomarkers Alliance (EIBALL) for ESR, please could you tell us about the subcommittee and your role?

I took on a 3-year term to chair this committee, and we set out a mission statement and a 2-year roadmap in the first instance. The mission is: "To facilitate imaging biomarker development, standardisation, and promote their use in clinical trials and in clinical practice by collaboration with specialist societies, international standards agencies, and trials organisations to develop a network of excellence." The 2-year roadmap has three pillars: 1) promoting biomarker usage in clinical trials; 2) setting standards for biomarker usage; and 3) educational activities that encourage the use of biomarkers in a standardised way within clinical trials. We are in the process of updating the roadmap for my third year. We maintain a policy of keeping the committee refreshed with new members to bring new insights and endeavours to achieve our mission.

Q2 Last year, EIBALL published a paper on validating imaging biomarkers for their use as decision-making tools. What was the reason behind the production of this paper?

The reason for making quantitative measurements is to be able to use the quantitation to drive clinical decisions regarding patient management. With any quantitation, it is important that the measurement is robust and reproducible wherever it is done, and that this does not vary because of variations in imaging hardware or software. We have to quality assure the measurement process and be aware of the confidence limits of the measurement. The purpose of the manuscript was therefore to discuss the necessary standards and set out recommendations for the imaging community when making quantitative measurements.

Q3 Collaboration is an essential part of scientific progression. Is the EIBALL subcommittee currently working on any projects with other committees or societies?

We work within an imaging community and collaboration is at the heart of what we do. Our biomarker inventory work is being done in collaboration with organ-specific specialist societies, for instance the European societies of urogenital radiology (ESUR), gastrointestinal and abdominal radiology (ESGAR), and breast imaging (EUSOBI). We work also with modality-specific societies and have members representing the European Society of Magnetic Resonance in Medicine and Biology (ESMRMB) and European Society of Hybrid Imaging (ESHI) on our subcommittee. We work with the European Society for Research and Treatment in Cancer (EORTC) to promote biomarkers within the clinical trials agenda. Finally, we have strong links with our North American partners from the Radiological Society of North America (RSNA) and have cross-representation on the EIBALL and their Quantitative Imaging Biomarker Alliance (QIBA) subcommittees. In particular, we are working with the QIBA metrology group to set standards for radiomic analyses and usage.

Q4 As co-director of the Cancer Research UK (CRUK) Clinical Magnetic Resonance Research Group at the Institute of Cancer Research (ICR), what are some of the projects that your research team work on?

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During my 16 years at ICR, the MRI group have conducted a research programme with many separate but integrated aspects. We had funding from CRUK (2004–2019) to achieve a programme of work that spanned preclinical and clinical research. It covered a variety of topics, with a primary focus on tumour heterogeneity. We aimed to understand how tissue heterogeneity related to differences in biological behaviour, to differences in response to combination therapies (with a focus on targeted therapeutics), and eventually to outcome.

Q5 Your research is primarily focussed on the use of MRI to identify biological indicators to predict a patient's prognosis and response to treatment. How has this field developed recently?

There has been a huge increase in the use of techniques such as diffusion-weighted MRI in tumour assessment, not just qualitatively, but also quantitatively, using metrics such as histogram parameters to characterise tumours and their response. Moreover, these data are available not just from dedicated regions, but with the advent of whole-body techniques, it has become possible to interrogate the entire skeleton, for example in patients with myeloma or skeletal metastases. Finally, the use of radiomics, which extracts data that is beyond visual perception from the images, will be a key methodology. It also lends itself to automated analysis, which is important as we move towards an era of artificial intelligence.

Q6 You have been noted as a pioneer for the use of endocavitary probes in MRI. How have these devices changed the approach to patient diagnosis and prognosis determination?

Endocavitary devices allow high-resolution imaging. They bring a receiver close to a region of interest and increase the signal in the region-of interest four to ten-fold. This allows a phenomenal improvement in image resolution, which is important when assessing early or small volume disease. We have used endorectal coils to assess prostate cancer, for which the technique has been particularly useful in following patients managed by active surveillance. These men

have tumours often not identifiable on standard imaging, and just being able to confirm their slow progression has been advantageous. Another major area has been in cervical cancer, for which high-resolution images of the cervix are particularly critical for mapping the extent of small tumours before the patients are considered for fertility-sparing procedures such as trachelectomy.

Q7 You are credited for bringing high-intensity focused ultrasound (HIFU) treatment to the patients at The Royal Marsden. What are the benefits of this treatment?

HIFU is a very precise treatment that works by thermally ablating tissue at its focus, causing narrow linear burns. It has been used mainly for treatment of symptomatic fibroids. In cancer, it is used for treating pain from bone metastases by ablating nerve endings in the overlying periosteum. Together with University Medical Center Utrecht, we ran an international trial sponsored by Philips (Best, the Netherlands) and showed that pain and quality of life did indeed improve in these patients. This had been preceded by a randomised trial in the USA which showed the same outcomes. University Medical Center Utrecht are now running an international trial comparing HIFU to radiotherapy for treating painful bone metastases. We are part of this consortium, which is funded by a European Union (EU) H2020 grant. We have also done some pilot work using HIFU to treat symptomatic recurrences of gynaecological malignancy. The trial has recently closed, and we are in the process of analysing the data.

Q8 You have previously worked in the Women in Academic Medicine Committee (WAM) and are currently a member of the Athena SWAN steering group. Why is this an important issue for yourself and how can other healthcare professionals support women in academic medicine?

Supporting women to be successful is very important to me. Women are generally more reticent in how they present themselves, and they often lack the confidence to promote themselves in the same way as their male counterparts. Society judges success by male behaviours, and although these conceptions are slowly changing, it takes a long time and has to be constantly worked at. Interestingly, the three countries doing well in the COVID-19 crisis are all led by women who recognised the problem early and put the right measures in place quickly: Germany, New Zealand, and Taiwan. Actions here were more critical than political manoeuvring, and women can often be more practical. Women in academic medicine can need a helping hand at the top end of the ladder; more appointments to chairman positions and lead roles would inspire other women as they become role models and mentors.

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Regulatory and Ethical Issues in the New Era of Radiomics and Radiogenomics

EDITOR'S PICK

The field of radiology is rapidly integrating radiomic and radiogenomic approaches into standard practice. The Editor's Pick by Pesapane explores the vitality of regulation and ethics when establishing and maintaining these pathways.

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Abstract

Radiomics is a science that investigates a large number of features from medical images using data-characterisation algorithms, with the aim to analyse disease characteristics that are indistinguishable to the naked eye. Radiogenomics attempts to establish and examine the relationship between tumour genomic characteristics and their radiologic appearance. Although there is certainly a lot to learn from these relationships, one could ask the question: what is the practical significance of radiogenomic discoveries? This increasing interest in such applications inevitably raises numerous legal and ethical questions. In an environment such as the technology field, which changes quickly and unpredictably, regulations need to be timely in order to be relevant. In this paper, issues that must be solved to make the future applications of this innovative technology safe and useful are analysed.

INTRODUCTION

In the current landscape of medicine, radiomics is an emerging translational field of research geared towards extracting mineable, high-dimensional data from radiological images with the aim to reach robust and reliable models that can be transferred into clinical practice for the purposes of prognosis, noninvasive disease tracking, and evaluation of disease response to treatment.[1,2] Through a similar process, radiogenomics investigates the relationship between the imaging characteristics of a disease, namely the imaging-phenotype or radio-phenotype, and its gene expression patterns, gene mutations, and other genome-related features.[3,4]

What is the practical significance of elucidating this relationship? Using innovative technology, radiogenomics aims to develop imaging

biomarkers that can predict risks and patient outcomes, allowing for better stratification of the patients and more precise management.[5]

TECHNOLOGIES BEHIND OMICS SCIENCES

Certain supporting technologies of radiogenomics can measure and quantify imaging features, whilst at the same time analyse the characteristics of a large family of genes, proteins, or even metabolites.[6] These technologies need large datasets,[7] nowadays defined as big data. The Cancer Imaging Archive[8] is an example of a service that hosts a large archive of anonymised medical images of cancer with related data (e.g., patient outcomes, treatment details, genomics, pathology, expert analyses) accessible for public download. This huge amount of information is data whose scale, diversity, and complexity would present difficulties in searching and analysis using the traditional data-processing methods.[9]

The method to analyse these data currently incorporates artificial neural networks, which are flexible mathematical models that use multiple algorithms to identify complex nonlinear relationships within big data. Machine learning (ML), a subfield of artificial intelligence (AI) science that allows computers to learn without being explicitly programmed, has been applied in radiogenomics.[10,11] Among the techniques that fall under the ML umbrella, deep learning (DL) has emerged as one of the most promising.[12] While ML commonly reaches an error rate that cannot be further lowered even with the addition of other data to the process, DL allows a continuous improvement towards a continuously better performance, namely a continually lower error rate.[13]

ETHICAL AND LEGAL CONSIDERATIONS IN RADIOMICS AND RADIOGENOMICS

The great enthusiasm towards and dynamism surrounding the development of software based on ML and DL is shown by the highly correlative trend of related publications in the literature in the last 10 years. Equally, there are no doubts that the use of radiogenomics represents a relevant topic for research teams, with initial promising results.[14,15]

Radiomics, using morphological features from radiological images, has been able to distinguish cancer from normal tissue and even define the histological grade for certain tumours.[16-18] Recent studies have been able to discriminate prostate cancer from benign prostate tissue (and even add information about aggressiveness through Gleason Score), as well as determine whether a meningioma was high or low grade.[19-21] Further examples of aggressiveness determination include a work regarding the use of radiomic assessment of pancreatic intraductal papillary mucinous neoplasm to stratify patients for surgical resection,[22] as well as a study that assessed the metastatic potential of lung cancer through 35 radiomic features.[23]

Radiogenomics investigates the relationship between disease imaging characteristics, namely the imaging-phenotype or radio-phenotype, and its gene expression patterns, gene mutations, and other genome-related features. Radiogenomics has already been utilised for identifying hepatocellular carcinoma subtypes more sensitive to immunotherapy,[3] and for work in breast cancer investigating a delicate situation such as that of neoadjuvant chemotherapy for locally advanced disease.[24]

However, radiomics and radiogenomics still need time before cementing a significant practical role in cancer research due to limitations of the available big data that, currently, lacks complete characterisation of the patients and poor integration of individual datasets.[9]

Moreover, in addition to the technical limits that are still to be addressed, some ethical challenges are straightforward and need to be guarded against. The intent behind the design of such studies needs to be considered to avoid unethical use, such as to perform clinical actions that would generate increased profits for suppliers (i.e., recommending drugs, tests, or medical devices) but not necessarily reflect better care.[25] Therefore, there is urgency for serious regulations and policy initiatives regarding the use of ML and DL systems for radiogenomics, especially when the correct detection of a disease's genomic background and the best management of a patient can be controversial.[9]

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As with AI, one of the most important issues to consider is classification.[9] If the software and algorithms used in radiogenomics are to be considered medical devices, a full set of specific legislations have already been developed and would apply.[9,26] If, on the contrary, these software and algorithms will not be classified as medical devices, it is vital to produce specific policies and legislation to regulate this growing field. There are two main approaches that could be taken in producing the necessary legislation: the precautionary principle approach imposes limits on certain applications of AI, ML, and DL systems due to their potential risks, while the permission-less innovation approach allows experimentation to proceed freely, and regulates issues that arise as they present themselves.[27] Clearly, the former would be beneficial for the diffused fear discussed below, whereas the second would allow enhanced research and both faster and impactful development.[28]

Furthermore, companies are improving their understanding of the potential of ML and DL, and are continuously collecting new types of data to process.[29] Therefore, serious regulations and policy initiatives concerning radiogenomics are a very hot topic, and the pursuit of one approach rather than the other will make a material difference. As far as we know, no governments have legislated about radiogenomics, despite the fact its applications are ready to change several national healthcare systems around the world.[9] Nevertheless, there have been some legal developments in the right direction. In 2016, the USA signed into law the 21st Century Cures Act, which is designed to help accelerate the development of medical products and encourage innovations and advances.[30] In addition, the Health Insurance Portability and Accountability Act (HIPAA) regulates data collection and processing in healthcare,[26] while the U.S. Food and Drug Administration (FDA) sets requirements in relation to cybersecurity[9,27] and is in charge of approving genome-based testing and radiomic studies.[30] In Europe, the European Union (EU) is now in the process of updating its data protection and cybersecurity legislation, with the General Data Protection Regulation (GDPR) and the Directive (EU) 2016/1148 on cybersecurity.[31]

The adoption of Regulation (EU) 2017/745 on medical devices and Regulation (EU) 2017/746 on *in vitro* diagnostic devices (IVDR) changed the European legal framework for medical devices, introducing new responsibilities for European Medicines Agency (EMA) and for national competent authorities.[32-34] This reform originated from the awareness that the existing directives created in the 1990s[32,34,35] were not fit to deal with new, evolving technologies such as AI systems, and from the identification of some flaws in this regulatory system, for example the lack of control on notified bodies. Some of the main characteristics of this reform will be the extended scope to include a wider range of products, extended liability in relation to defective products, strengthening of requirements for clinical data and traceability of the devices, more rigorous monitoring of notified bodies, and improved transparency through making information relating to medical devices available to the public.[9,36]

However, considering the thousands of algorithms that will likely be developed, governmental regulatory agencies are ill-equipped to perform regulations in this field internally.[37-41] Moreover, the sheer number of algorithms that will likely be submitted for regulatory approval could place considerable burdens on the regulatory reviews process. Therefore, public–private partnerships between regulatory agencies and trusted organisations such as medical specialty societies could play an important role in validation of AI algorithms, collecting the real-world evidence that support the ongoing efficacy and safety of AI algorithms in clinical practice.[37-42]

Although the gap of clear regulation could seem a problem for the future, this might change in a few years. One relevant example is the insurance system, which might discriminate patients with medical conditions that are determined to be predominantly genetic and not lifestyle related. Recently, an insurance provider in the USA announced that it will no longer offer policies that do not include digital fitness tracking that collect health data through wearable devices such as a smartwatch. Policy holders can earn discounts and rewards such as gift cards for hitting exercise targets and activity-tracking devices can record how much exercise somebody is doing and can be used to log dietary choices.[43] Although the efficacy, in terms of benefits, of interventions that use apps to

improve diet, physical activity, and sedentary behaviour have been demonstrated,[44] some privacy advocates may warn that insurers could use tracking data to punish customers who fail to meet targets,[45] however it is the belief of the author that this is not the biggest issue to face. Foreseeing the future applications of radiogenomics, which laws do governments have to implement in order to prevent insurance companies from requesting the genetic profile of their customers before stipulating a contract? In this dystopian scenario, insurance companies may provide patients with insurance assuming they are allowed access to all of the patient's data, including radiogenomic data. Based on this, companies may decide to set patients' premiums based on their own genome.

On the other hand, is it true that genome sequencing reveals a patient's fate? Many people fear that healthcare might attempt to 'play creator' with the use of genome sequencing or gene modification. Despite radiogenomics being capable of revealing possible health conditions and risks for some diseases, we must remember that our health is not entirely determined by our genome.[46] For this reason, the aim of radiogenomics is not to identify a predisposition to a disease, but to detect the genetic alterations of a disease once it has already manifested itself in order to choose the most precise treatment and improve the patient's outcome, otherwise known as precision medicine.

Nevertheless, nowadays there is diffuse fear about this approach. As in earlier historical eras, the origins of fear stem from the lack of knowledge and experience with the particular technology. It is the author's belief that this gap of knowledge can be filled by the one who is responsible for this kind of investigation, namely the radiologist.[7,37,47] In the past, shortly following Wilhelm Conrad Röntgen's discovery of the X-Ray, people were scared that this technology might read their thoughts and see through their body and soul.[13] Since then, radiologists have been on the wave front of the digital era in medicine. In being the first medical professionals to pioneer the adoption of computer science in their daily work, they are now arguably the most digitised arm of healthcare professionals.[48,49] Even though the introduction of new technologies has mostly been perceived as new approaches for producing images, innovation has also deeply changed ways to treat, present, and interpret images.[49,50] Moreover, the role of radiologists will be enhanced by radiogenomics if they choose to embrace this technology for acquiring more information regarding an imaging finding, including those not only pertaining to diagnosis but even features which are useful for treatment and prognosis.[5,16,51-53] This technology may also be used for saving time they currently give to routine and monotonous tasks, with a strong volition to dedicate the saved time to communicate with patients and to interplay with colleagues in multidisciplinary teams.[50]

Similarly, forward-looking legal notions and principles will be necessary for the near future, as the first scenarios with narrow AI and clinical applications of radiomics and radiogenomics may arrive as early as within a year at the medical malpractice law firms. Healthcare regulators, agencies, and lawyers need to face these new challenges.

DATA PROTECTION AND CYBERSECURITY ISSUES

Data protection and cybersecurity implications of the radiomic data represent another challenge that needs to be addressed. An ongoing debate about balance between privacy and the need to obtain a large amount of data is developing, especially when it comes to sensitive data such as medical information.[9,13,47] As discussed above, the lack of appropriately organised big datasets for training radiogenomic algorithms is a key obstacle preventing the introduction of these systems in healthcare.[7,11,54,55] One of the problems is that sensitive data should be collected from unknown sources[56] because of the lack of unique and clear regulations.[57,58] In the era of electronic medical records, radiogenomics complicates an already complex cybersecurity landscape;[59] the concept of confidentiality requires that a physician withholds information from the medical record in order to truly keep it confidential.[25]

A possible solution for cybersecurity could come from blockchain technology (BCT), namely an open-source software that allows the creation of large, decentralised, and secure public databases containing ordered records arranged in a block structure.[60] Different blocks are stored digitally, in nodes, using the computers of the blockchain

network members themselves, who are both users and maintainers of the entire system. The information on all transactions, present and past, are stored in the nodes.[61] Although the best-known use of BCT is in the field of economics (i.e., cryptocurrencies), its usefulness is extending to other fields, including healthcare. Particularly, BCT appeals to radiogenomics due to its emphasis on sharing, distribution, and encryption.[61] Newer BCT efforts such as smart contracts, second-layer systems, and permissioned blockchains further the potential healthcare use, and there has been limited hype surrounding the potential of the technology in medicine.[62] As the blocks are impossible to change, it is impossible to delete or to modify anything without leaving a trace, and this is critical in the case of sensitive data such as medical information.

Unfortunately, there is another side of the coin: at this moment, to obtain greater security, the privacy is lost. The patients should accept to share their sensitive data, without a central authority to decide what is right or wrong. The author's opinion is that the time is not yet ripe for such an eventuality. This is also because BCT currently guarantees integrity of patient information but not the privacy security, meaning further development needs to be considered before healthcare application.

CONCLUSIONS

These innovative technologies that rely on sensitive data to improve patient care and treatment are needed. However, several challenges such as the regulation of data protection and cybersecurity, the new policy initiatives, and the discussion about the fiduciary relationship between patients and medical systems will have to be addressed as soon as possible. A good employment of radiogenomics may be helpful, powerful, and valuable. Vice versa, an unethical use of this technology may be dangerous: regulatory authorities, scientists, physicians, and patients must work together to prevent this.[55] The most important means of dissolving fears around radiogenomics is education; this is the time to discuss and debate how technologies such as radiogenomics will change our lives and what are the things we do not want to happen.

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New Frontiers in Placenta Tissue Imaging

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Abstract

The placenta is a highly vascularised organ with unique structural and metabolic complexities. As the primary conduit of fetal support, the placenta mediates transport of oxygen, nutrients, and waste between maternal and fetal blood. Thus, normal placenta anatomy and physiology is absolutely required for maintenance of maternal and fetal health during pregnancy. Moreover, impaired placental health can negatively impact offspring growth trajectories as well as increase the risk of maternal cardiovascular disease later in life. Despite these crucial roles for the placenta, placental disorders, such as preeclampsia, intrauterine growth restriction, and preterm birth, remain incompletely understood. Effective noninvasive imaging and image analysis are needed to advance the obstetrician's clinical reasoning toolkit and improve the utility of the placenta in interpreting maternal and fetal health trajectories. Current paradigms in placental imaging and image analysis aim to improve the traditional imaging techniques that may be time-consuming, costly, or invasive. In concert with conventional clinical approaches such as ultrasound, advanced imaging modalities can provide insightful information on the structure of placental tissues. Herein, the authors discuss such imaging modalities; their specific applications in structural, vascular, and metabolic analysis of placental health; and emerging frontiers in image analysis research in both preclinical and clinical contexts.

INTRODUCTION

The placenta plays numerous critical roles during pregnancy, from modulating adaptations of maternal cardiovascular, skeletal, and endocrine systems, to controlling transport of nutrients, oxygen, and waste between maternal and fetal circulations. Impaired development and/or function of the placenta can result in adverse maternal and fetal clinical outcomes. With respect to the development of advanced diagnostic tools and treatment options that can potentially inform and improve clinical practices, noninvasive biomedical imaging of the placenta provides a promising approach. Herein, the authors discuss imaging modalities that can be used to generate insight into anatomical structure, vascular physiology, and metabolism of the placenta (Figure 1).[1-5] For example, multiple modalities are now available that can be used to study placental blood flow, maternal-placental and fetoplacental vasculature, placental microcirculation, the spatial pattern of fetoplacental density, placental sufficiency, intrauterine hypoxia, placental oxygenation, and haemoglobin oxygenation in normal and pathological conditions. Additionally, the increased value and analytic depth of multiparametric three-dimensional (3D) computational image analysis methods that accompany these imaging modalities are discussed in detail. Finally, in the last section of this review the authors discuss how advanced computational approaches such as computer vision, automation, and deep learning strengthen the power of preclinical and clinical biomedical imaging data.

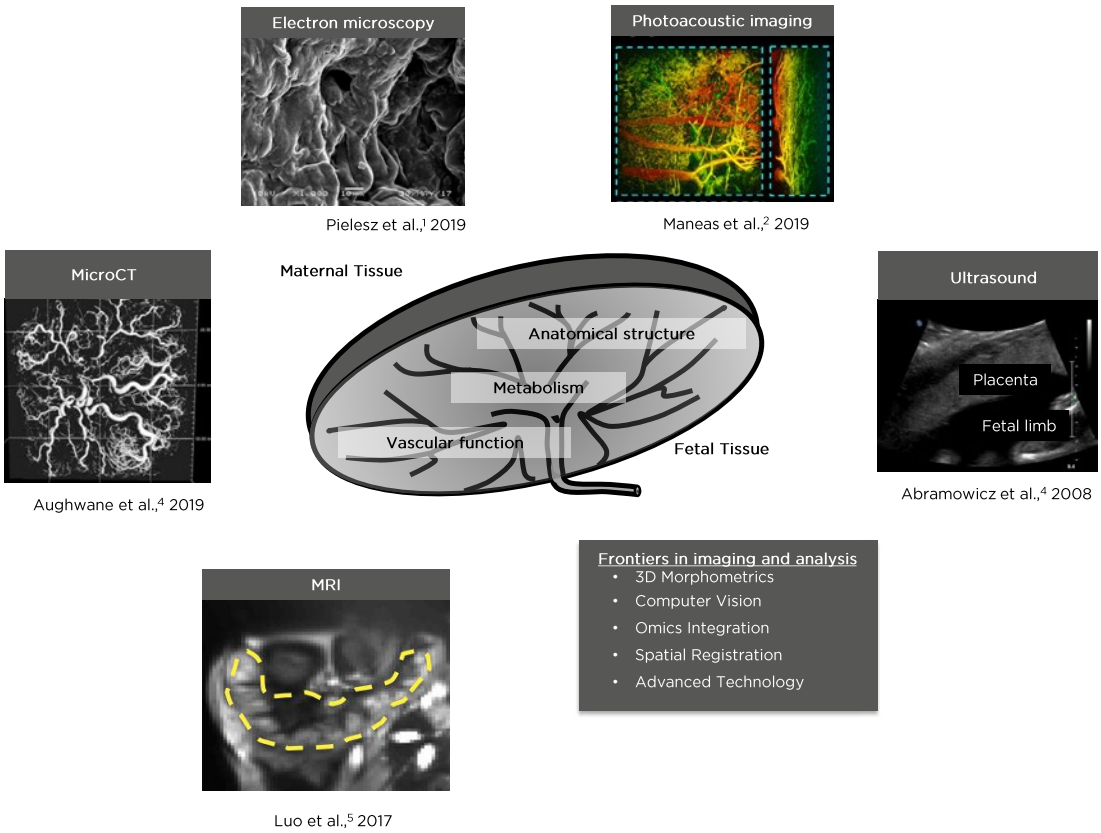

Figure 1: Examples of imaging modalities that can be used to generate insight into anatomical structure, vascular, and metabolic function of the placenta.[1-5]

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Structure

Detection of abnormalities in placental structure is clinically important because it allows clinicians to diagnose symptoms early in the pregnancy and develop individual treatment responses.[4] These structures include the boundaries of different placental compartments, the size and volume of the placenta and extraembryonic tissues, and the overall location of these structures with respect to one another. Microfocus CT (microCT) is a fast-growing imaging technique that can provide high-resolution, large field-of-view 3D morphological structures of the placenta. Its use in quantitative analysis of the fetoplacental vascular tree and the feasibility for obtaining this information on human samples with the aim of understanding complications of intrauterine growth restriction (IUGR) has been demonstrated *ex vivo*.[6] In a complementary *ex vivo* study, Pratt et al.[7] compared two contrast agents by their capacity to produce superior image quality for improved measurements of placental vascular density and analysis of the vascular tree structure, and determined MICROFIL® to be the better contrast agent for this application. Despite the capabilities of microCT to generate non-destructive high-resolution images, this modality cannot be used for human placental imaging *in vivo* because of its use of an ionising source, but it remains an invaluable tool for preclinical or clinical *ex vivo* quantification of morphology and vascularity.

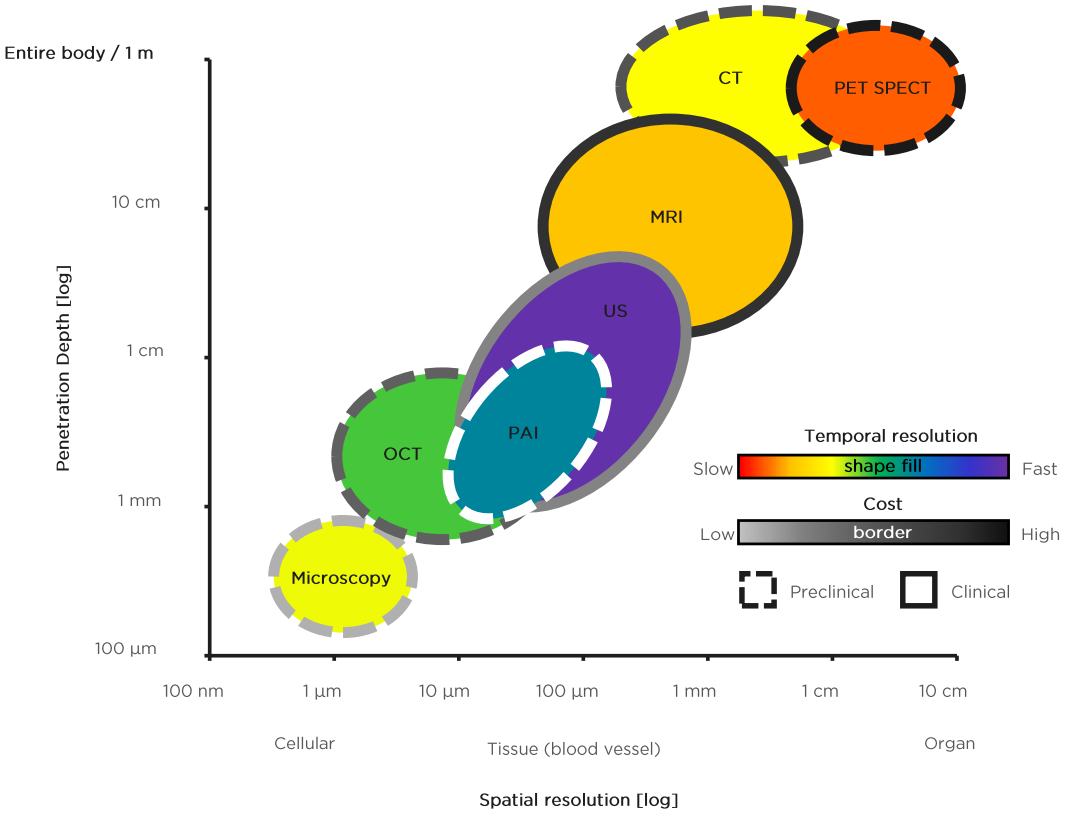

Figure 2: Schematic representation of spatial resolution versus penetration depth of various preclinical (dashed border) and clinical (solid border) imaging modalities used for placental and extraembryonic tissue imaging. The temporal resolution is represented by a pseudo-colourmap, with red representing slow and violet representing fast. The cost is represented by a different pseudo-colourmap, with grey representing low cost and black representing high cost. Note that photoacoustic imaging has a dashed white border which represents its primary use in preclinical studies but has yet to be clinically used in any form. Given the absence of clinical applications for photoacoustic imaging, associated costs for this technique are not included.

Non-ionising techniques such as MRI, which provides better soft-tissue contrast, or ultrasound (US), which provides higher throughput real-time images, are more commonly used in preclinical and clinical studies. Lax et al.[8] and Teo et al.[9] provided three easily identifiable *in vivo* features useful in diagnosing placental invasion in T2-weighted MRI images: 1) lower uterine bulging; 2) heterogenous placental signal intensity; and 3) dark linear intraplacental bands. However, MRI is best used as an adjunct to US, particularly when the US resolution is diminished as a result of obesity or a posteriorly situated placenta. Furthermore, as shown in Figure 2, US is low-cost compared with MRI and is advantageous for longitudinal studies to monitor fetal growth and changes in placenta function. In a retrospective *in vivo* US study, Rac et al.[10] developed a predictive equation of placental invasion termed placenta accreta index, which relies on the number of prior caesarean deliveries and several US parameters including smallest myometrial thickness, lacunar spaces, and the presence of bridging vessels. Additionally, alongside placental compartments, US can be used to image the umbilical cord insertion point. For example, Wax et al.[11] determined that cord insertion-to-placental edge distance could be used to diagnose marginal cord insertion and risk for prelabour rupture of membrane, preterm prelabour rupture of membrane, extreme umbilical cord lengths, and spontaneous preterm birth as described by Ebbing et al.[12] With respect to structural assessments, US followed by MRI is the preferred methodology overall to obtain structural tissue contrast, but further studies directly comparing the specificity and sensitivity of the two are needed.

Vascular Function

Normal fetal growth requires sufficient oxygen and nutrient delivery through the placenta. Therefore, quantification of maternal–fetal perfusion and vascular function is crucial in diagnosing placental abnormalities. Historically, preclinical *ex vivo* microscope analysis has dominated interpretation of placental vascular development and function. For example, Coan et al.[13] performed stereological analysis on mouse placentas to quantify the development of the labyrinth zone, which serves as the nutrient transport barrier and mediator between the maternal and fetal circulatory systems. Furthermore, these methods support predictions of the diffusion capacity of oxygen. In general, postmortem microscope analysis can provide high-resolution images for modelling of placental vascular function, but to clearly predict the health of the fetus and understand the functional interdependence of the maternal–placental–fetal triad, longitudinal monitoring is needed because *ex vivo* microscopic analysis is not sufficient.

Functional MRI can address the need for longitudinal monitoring by providing online monitoring of blood flow using blood oxygen level dependent (BOLD). In a study by Sørensen et al.,[14] dark and bright areas corresponding to the fetal and maternal side, respectively, in BOLD placental images during normoxia and hyperoxia were compared. BOLD signal increased as darker areas became brighter, which is indicative of increased placental oxygenation. Thus, a reduced or constant placental BOLD signal during hyperoxia may be associated with impaired placental function and poor neonatal outcome. Furthermore, BOLD images of the placenta acquired over time can be used to generate time-to-plateau maps, which can aid in identifying regional heterogenous oxygenation in the placenta.[5] This promising biomarker had relatively homogenous values near zero under normoxia conditions, while placentas under maternal hyperoxia displayed inhomogeneous delayed values. Indeed, multiple studies concluded that maternal hyperoxia induces the hyperoxic BOLD effect, which is an increase in placental signal intensity in T2-weighted images as reviewed by Sørensen et al.[15] In pregnancies complicated by IUGR, similar effects were observed with a significantly increased BOLD effect compared with control cases. However, the authors noted that the BOLD effect is a relative measurement and that an increase in BOLD signal may originate from a reduced T2-signal baseline rather than an increased absolute signal. A baseline T2-signal may therefore be a sufficient initial clinical biomarker for detecting dysfunctional placentas.

Online monitoring of blood flow can additionally be accomplished using arterial spin labelling (ASL) MRI. Using pseudocontinuous ASL MRI, Liu et al.[16] generated four perfusion-related parameters: placental volume, placental blood flow (PBF), high PBF (hPBF), and relative hPBF. In a longitudinal study, patients with ischaemic

placentas showed significant decreases in hPBF and relative hPBF values compared with controls, suggesting its promise as a biomarker for predicting placental ischaemia. By monitoring placenta perfusion, diseases such as IUGR or congenital heart disease (CHD) have been linked to dysfunctional placentas. For example, placental perfusion velocity-selective ASL (VSASL) MRI measurements have value for predicting fetal CHD.[17] In fetal CHD pregnancies, variation in regional placental perfusion significantly increased while global placental perfusion significantly decreased with advancing gestational age. Overall, functional variants of MRI can quantify maternal–fetal perfusion. However, MRI variants that rely on the aid of exogenous contrast agents (contrast enhanced [CE] MRI), such as gadolinium, are not approved for human use because of its dissociation into toxic form.[18] Therefore, similar to structural MRI, functional MRI, but not CE MRI, may be used as an adjunct to functional US to clinically evaluate vascular function.

CE US (CEUS) enables imaging of structures with low perfusion by employing the use of gas-filled, lipid-encapsulated microbubbles to increase contrast because of the acoustic impedance mismatch from surrounding tissue. In an *in vivo* study by Roberts et al.[19] to assess the safety of CEUS for studying placental perfusion in rhesus macaques and human subjects, placental structural damage was not observed after multiple CEUS examinations. Additional results of the examinations in human subjects demonstrated visualising placental perfusion in as early as 11 weeks.[19] As a clinical continuation of this work, Roberts et al.[20] used CEUS to assess maternal blood flow into the intervillous space and reported the detection of maternal perfusion through the spiral arteries in as early as 6 weeks. This suggests that remodelling of extravillous trophoblast cell clusters to reduce flow resistance into the intervillous space may be a progressive process that occurs earlier than previously suspected.[20] Doppler US imaging is traditionally used to quantify the maternal–fetal blood flow.[21] Uterine artery Doppler, a combination of pulsed and colour Doppler features, can be used to measure the human maternal–fetal blood flow to show that most early IUGR cases display abnormal waveforms, which is associated with coexisting preeclampsia and maternal–placental vascular malperfusion.[22] Furthermore, uterine artery Doppler in combination with multiple maternal serum markers can be used to predict the development of preeclampsia.[23,24] With respect to high-risk pregnancies, Doppler US has been supported to reduce the risk of perinatal deaths with potentially fewer obstetric interventions.[25] Further studies correlating fetal development to maternal–fetal blood flow are required and could provide invaluable insights into developing therapies for placental malfunction.

Metabolism

Irregularities in cellular metabolism have shown to be surrogate markers of disease. In the case of obesity, Calabuig-Navarro et al.[26] have proposed that the metabolic capacity of the placenta plays a central role in regulating fetal adiposity and conferring disease risk to offspring. Indeed, placental fatty acid esterification and mitochondrial fatty acid β-oxidation associate with markers of fetal adiposity in the context of maternal obesity.[26] Mechanistically, this may relate to the interaction between fatty acid oxidation, mitochondrial function, and oxidative stress.[27] Thus, it may be insufficient to strictly perform structure and vascular imaging. Metabolic imaging is a relatively new field that observes and tracks changes in metabolic pathways that may be linked to various clinical conditions. Quantification of the placental metabolic capacity, in addition to structure and vascular function, can lead to a better understanding of the interaction between placental function and fetal development. For example, Austin et al.[28] elaborated on the importance of evaluating the spatial distribution of elemental metal species and their role in metabolic processes, such as oxygen transportation and mitochondrial function. Deficiencies in these essential metals and/or long-term exposure to exogenous heavy metals are associated with the negative health of a child. A predominant methodology that can be used to obtain placental metabolic data is proton magnetic resonance spectroscopy (^{1}H-MRS). In a clinical *in vivo* study, Denison et al.[29] used ^{1}H-MRS to measure the choline-lipid ratio in severe cases of placental insufficiency that were associated with IUGR. Current evidence suggests that a reduction in placental choline peaks is associated with poor cellular turnover; therefore, the choline-lipid ratio may be used as a novel biomarker

to detect impaired placental function. Song et al.[30] performed a similar study in which they proposed to combine the choline-lipid ratio with apparent diffusion coefficient values from diffusion-weighted MRI to enhance the sensitivity and specificity of detecting IUGR. Compared with the data presented by Denison et al., the lipid peaks in the present study significantly increased with IUGR severity. The discordance in these findings may relate to the population-based differences in the severities of IUGR in these two studies.

To further understand the involvement of metabolism in placental abnormalities, variants of Raman spectroscopy, a label-free method based on Raman scattering that provides the molecular structure of the sample, can be used. Thus far these studies have been largely restricted to *ex vivo* studies. Pielesz et al.[1] tested the application of Fourier transform Raman spectroscopy to identify spectroscopic biomarkers or specific frequency ranges that may accurately indicate the transport efficiency governed by syncytiotrophoblast. The most notable region observed was the 950–750 cm^{-1} frequency range, which represented changes in molecular structure to differentiate healthy from pathological tissue. Using micro-Raman spectroscopy, Chen et al.[31] studied the metabolic variation in preeclamptic placentas. Compared with normal placentas, preeclamptic placentas displayed higher amplitudes at peaks assigned to the tryptophan indole ring and phenylalanine, which suggest a significant reduction in the ordered structures of the proteins as well as damage to the amino acid side chains. Overall, these studies support the notion that Raman spectroscopy is effective in differentiating healthy from pathological placental tissue and therefore can be used to increase the diagnostic accuracy of placental insufficiency.

NEW FRONTIERS IN PRECLINICAL IMAGING

One major need in placental imaging is to understand the dynamic changes in blood oxygen saturation and vascular perfusion *in vivo* without the use of exogenous contrast agents. To address this, several advances have been made towards photoacoustic imaging (PAI), an imaging modality that combines US with the high-molecular sensitivity of optical imaging to measure changes in oxygen saturation by exploiting the different absorption spectrums of oxy- versus deoxyhaemoglobin in the placenta.[32] Extracting the saturation level involves fitting the PA intensity to the optical absorption of haemoglobin at various excitation wavelengths.[33] Using PAI in a rat and mouse study, Lawrence et al.[34] and Yamaleyeva et al.,[35,36] respectively, measured placental hypoxia and evaluated its association with the progression of preeclampsia or IUGR due to ischaemia. Key challenges that must be addressed prior to clinical translation of PAI are limited light delivery to deep fetal tissues and safety limits of nanosecond pulsed radiation exposure for developing tissues.

In addition to translating technology for clinical trials, preclinical studies support investigation of the relationship between placental biology and embryonic development through the use of models with short gestation periods and homogeneous genetic traits. Yadav et al.[37] used dynamic CE MRI to quantitatively study the gestational age-dependent perfusion changes and vascular diameters in the regional compartments of normal murine placenta. With advancing gestation, the maternal central canal diameter increases, which may contribute to an increase in placental perfusion. In a separate longitudinal study by Krishnamurthy et al.,[38] T2-weighted MRI signals were measured with advancing gestational age. With advancing gestation, T2 relaxation times decreased in both high and low perfusion zones with absolute T2 signal values in low perfusion zones matching the whole placenta.

To address aspects of placenta biology that are specific to primates, extensive, ground-breaking research has been performed on nonhuman primate models, such as the rhesus macaque, a more clinically relevant translational animal model establishing the maternal–fetal–placental unit function during pregnancy.[39] In a placental perfusion study of rhesus macaques, BOLD and dynamic CE MRI placental images were compared to create a model connecting the observed T2-weighted images to a modified BOLD signal parameter that relates the intervillous blood flow and oxygen exchange with the fetal vasculature.[40] Furthermore, with the aid of contrast agents, Lo et al.[41] used Doppler US with dynamic CE MRI to detect IUGR in nonhuman primate models. T2-weighted MRI and anisotropic

water diffusion images of the fetal brain *in utero* were acquired to characterise the aberrant effects of IUGR on fetal neurodevelopment, such as reduced brain volume. Several new contrast agents are being developed to obtain specific molecular information for these imaging techniques, such as MRI, US, and optical techniques; however, these agents still need to be evaluated thoroughly prior to clinical translation.[42-44] Overall, longitudinal preclinical studies play a crucial role in translating these technological advancements to the clinic.

FUTURE OF IMAGING

Computer Vision

Computer vision techniques provide a particularly promising new frontier for the evaluation of placental physiology and structure–function relationships. These techniques make use of certain features to numerically describe physical properties of the placenta, which, once determined, can be used to test for correlation between clinical characteristics of the pregnancy as well as clinical maternal–fetal outcomes. For example, placental maturity and gestational age have been tested in US and MRI images with positive results. Specifically, grey-level co-occurrence matrix texture features, known as Haralick texture features, have been used to show an increase in placental heterogeneity throughout the gestational age.[45,46]

Image analysis is increasingly combined with machine learning techniques that provide prediction models for examining correlation between clinical characteristics and outcomes. A multitude of machine learning and clustering methods, including Naïve Bayes, K nearest neighbors, k-means, and multilayer perceptron, have been successfully used alongside texture analysis techniques for MRI and US images. For example, Romeo et al.[47] used machine learning methods with MRI-derived texture analysis features to assess the presence of placenta accreta spectrum in patients with placenta praevia with an accuracy up to 98%. Using an alternative segmentation approach, Gupta et al.[48] applied wavelet decomposition-based conditional random fields to successfully develop segmentation methods for US images of the fetus. These tools could potentially be applied to placenta segmentation using proper constraints and choice of the training set features.

Morphomics

Morphomics is a recently coined term that involves quantitative measurements generated via image analysis software and scientific visualisation tools. These analytic morphomics aid in personalised care by stratifying the image analysis data with respect to disease status. Compared with platform-dependent and specialised commercial software used in clinical settings, a wide range of open-source, free, and customisable software tools are available for morphomic analysis. ImageJ is an open-source software that became popular as a result of its large repository of plugins and macros, including 3D viewer plugins, developed by the userbase for different tasks and image formats.[49] Quantitative analysis of villi anatomy in the placenta, molecule transportation across the maternal–fetal interface, and analysis of volumetric data to study placental microcirculation, such as the spatial pattern of fetoplacental vascular density, is possible with these tools.[3,7,50-52]

Insight Segmentation and Registration Toolkit (ITK) provides software developers with a large collection of image segmentation and registration algorithms, which are widely used for implementing custom software for specific medical imaging problems.[53] Two ITK-based tools that gained popularity among researchers are ITK-SNAP for visualisation and segmentation of 3D images to aid in analysis of placental form and function calculations, and Elastix for image registration.[5,54,55] Using Elastix, You et al.[56] developed a semiautomated method for segmentation of the maternal and fetal compartments of the placenta using intravoxel incoherent motion. Finally, the large community-supported 3D Slicer software with a user-friendly interface[57] was used by Looney et al.[58] to fully automate the segmentation of 3D placenta US data. 3D Slicer additionally supports registration, segmentation, and annotation, as well as scripting functionalities for batch-processing in Python. The design allows users to easily customise 3D Slicer by adding modules or extensions developed by the community to address specific imaging modalities or analysis tasks, such as studying fetal development or modelling placenta villi.[59,60] SlicerMorph, an actively

developed extension for 3D Slicer, provides biologists with the morphometric analysis tools for 3D volumetric and surface data, such as semi-landmarking and Generalized Procrustes Analysis (GPA) for population-level analysis.

CONCLUSION

US is the gold standard for non-ionising noninvasive imaging used to assess placental structure. However, US alone is not sufficient to fully characterise placental pathophysiology, including vascular and metabolic functions and their relationship to clinical maternal and fetal outcomes. Emerging imaging modalities such as PAI are gaining popularity because they can be transparently integrated with existing imaging systems including US. Another useful clinical non-ionising modality discussed above in detail is MRI and its variants, including diffusion-weighted, BOLD, and ASL, which have been studied to provide unique biomarkers to determine placental abnormalities. With respect to unravelling the role of metabolic heterogeneities in placenta health, several biomarkers have recently been discovered and studied using various technologies, such as ^{1}H-MRS and Raman spectroscopy. Finally, to accurately quantify data generated by these imaging modalities, in terms of both 3D visualisation and multiple quantitative parameters, computer vision methods for quantitative image analysis are emerging. Various open-source platforms are being explored to develop analytical morphomics that can eventually predict effects on fetal growth based on dynamic changes in placental health and function. The recent explosion of image analysis and machine learning strategies will enhance both the quality and quantity of data available for making accurate diagnosis and monitoring therapeutics towards maintaining a healthy placenta. The clinical translation of these new frontiers is greatly needed to aid in the detection and diagnostic accuracy of placental abnormalities, reduce the risk of perinatal deaths, and improve the long-term course of offspring developmental health.

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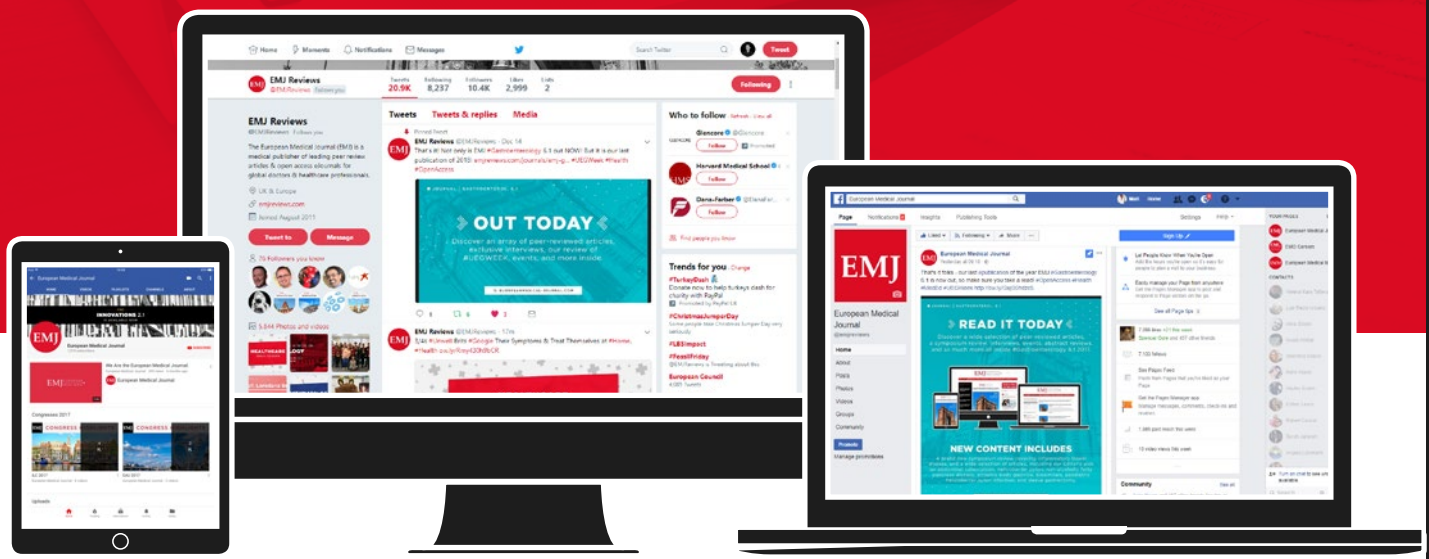

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Translingual Neural Stimulation With the Portable Neuromodulation Stimulator (PoNS®) Induces Structural Changes Leading to Functional Recovery In Patients With Mild-To-Moderate Traumatic Brain Injury

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Disclosure: Dr Tyler, Dr Danilov, and Dr Kaczmarek are co-founders of Advanced Neurorehabilitation, LLC, which holds the intellectual property rights to the PoNS® technology. Dr Tyler is a board member of NeuroHabilitation Corporation, a wholly-owned subsidiary of Helius Medical Technologies, and owns stock in the corporation. The other authors have declared no conflicts of interest.

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Abstract

Traumatic brain injury (TBI) of varying severity can result in balance and movement disorders, for which the benefits of treatment with physical therapy has limits. In this study, patients with post-TBI balance issues received translingual neural stimulation (TLNS) in concert with physical therapy

and the effects on the grey matter volume (GMV) were evaluated. TBI-related balance and movement impairments were also assessed through Sensory Organization Test (SOT) and Dynamic Gait Index (DGI) scoring. When comparing pre- and post-intervention results, the most prominent GMV changes were increases within the cerebellum, and temporal regions, which are involved in automatic processing of gait, balance, motor control, and visual-motion. Decreases of GMV in frontal, occipital lobes (involved in less automatic processing or more conscious/effortful processing of gait, balance, motor control, and vision) positively correlated to increases in SOT/DGI scores. These results indicate that TLNS can produce brain plasticity changes leading to positive changes in functional assessments. Overall, these data indicate that TLNS delivered in conjunction with physical therapy, is a safe, effective, and integrative way to treat TBI.

INTRODUCTION

The Centers for Disease Control and Prevention (CDC) report that up to 5.3 million people in the USA are living with a disability related to traumatic brain injury (TBI),[1] resulting in $76.5 billion per year[2] in medical and rehabilitation costs. The majority of TBI are considered mild-to-moderate (mmTBI)[3] and development of balance impairments after injury is common, occurring in 30% to 65% of patients.[4] Currently, the main approach for treating mmTBI symptoms is physical therapy (PT), but its effect has limits and improvements in function are often lost if therapy is not sustained.[5] Recent studies have demonstrated the effective outcomes with motor-behavioural interventions and cognitive skill training after injury,[6-9] which support the development of a unified and multidisciplinary approach to mmTBI treatment.[10-12]

A treatment plan utilising translingual neural stimulation (TLNS) combines electrical stimulation of cranial nerves V (trigeminal) and VII (facial) with physical therapy mainly aimed at restoring balance and gait.[13] TLNS can be provided via the Portable Neuromodulation Stimulator (PoNS®, Helius Medical Technologies, Newtown, Pennsylvania, USA), an investigational medical device that delivers sequenced patterns of electrical stimulation on the tongue. These stimuli then trigger the trigeminal and facial nerves to excite a natural flow of neural impulses to the brainstem or cerebellum and promote changes in targeted brain structures.[14-16] Results from pilot studies of TLNS treatment of patients after mmTBI suggest that, in the absence of identifiable tissue damage, a combination of neurostimulation and rehabilitation that is both targeted and challenging will induce neuroplastic changes (i.e., brain regions of pons, brainstem, and cerebellum), reduce symptoms, and begin normalising function.[13,14,16,17] In TLNS, stimulation of the tongue can occur with either a high-frequency (HFP) or low-frequency (LFP) pulse device. A long-term clinical trial was recently completed to investigate the efficacy of TLNS in patients with mmTBI symptoms and compare outcomes of the HFP and LFP devices.[18]

To better understand the effects of TLNS, the substudy presented here was developed with the primary objective of using structural MRI (sMRI) to evaluate cortical and subcortical changes in the brains of patients before (pre-) and after (post-) treatment. Specifically, the grey matter volume (GMV) results before and after treatment were compared to investigate if individuals experienced a reduction in compensatory brain regions and, conversely, growth in deficient automatic brain regions. These structural changes were then correlated to behavioural assessments of balance and gait before and after treatment.

METHODS AND MATERIALS

Participants

Participants were recruited through print and radio advertising and were required to have mm TBI that occurred 1 year before enrolment, reached a functional plateau in their recovery (as defined by a discharge note from their physical therapist), and a NeuroComa Sensory Organization Test (SOT) composite score 16 points below normal after adjustment for age. Mild and moderate TBI diagnoses were made based on guidelines established by Veterans Affairs/Department of Defense.[19] All participants had a nonremarkable neuroradiographic report

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after their most recent TBI, meaning that the findings were not significant per the clinical judgement of the neuroradiologist. Reports were reviewed to rule out refractory subdural haematomas, evidence of tumours, anatomical anomalies, or evidence of loss of grey matter. Neuroradiographic reports and therapy discharge notes were obtained through a medical records request; MRI prior to enrolment was required if a participant lacked a neuroradiographic report. Potential participants were excluded if they had oral or other health problems that would preclude TLNS or, in the opinion of the investigators, were unable to successfully complete the stimulation intensity level setting procedure for the device. Additional inclusion and exclusion criteria are available (please see next paragraph for the detailed criteria for inclusion and exclusion about all the nine mmTBI participants who received HFP or LFP stimulation). Rolling recruitment was used, and enrolled participants had a unique 3-digit identifier that was used for double blinding and 1:1 randomisation by a clinical monitor.

Nine participants with mmTBI (at least 1 year post-injury) were involved (age range: 43–62 years; mean age: 53.11; standard deviation: 6.60; 6 female and 3 male) in the study. The Institutional Review Board (IRB) at School of Medicine and Public Health, University of Wisconsin–Madison, Madison, Wisconsin, USA, approved all aspects of this study, and all the nine participants were recruited on a voluntary basis, signed the approved consent form before beginning of the study. They completed consent, screening, and informational forms during their first visit and the informed written consent was obtained from all participants. All participants who chose to enrol in the TBI study were also offered the opportunity to enrol in the MRI substudy.

Moreover, all nine participants received HFP or LFP stimulation, and the detailed criteria for inclusion and exclusion were: participants able to walk independently for at least 20 minutes, had access to a treadmill while not in the clinic, and had no changes in their medications for at least 3 months prior to participation Exclusion criteria included oral health problems, nonremovable metal orthodontic devices, or oral cavity piercings that could interfere with TLNS use, chronic infectious disease, unmanaged hypertension, diabetes, neurological disorders other than those attributed to their primary diagnosis, history of treatment for cancer other than basal cell carcinoma within the past year, a penetrating head injury, craniotomy, or refractory subdural haematoma. Long-term use of psychoactive or psychostimulant medications that, in the opinion of the investigators, would compromise the participant's ability to comprehend and perform study activities was also grounds for exclusion, as was the presence of a pacemaker or elevated risk for cardiovascular events. Individuals with a lower extremity biomechanical prosthetic, history of seizures, or a 'severe' score in any of the attention, memory, or executive functions categories on the Cognitive Linguistic Quick Test (CLQT) were also excluded.[20]

Intervention

The intervention TLNS training programme focussed on balance and gait, and consists of twice-daily in-lab training for 2-weeks (with at-home training during the intervening weekend). The participants also received physical exercise training to develop improved motor coordination and mobility as part of the TLNS training. All participants returned to the clinic weekly during the at-home phase for a single session of retraining and progression, and participated in periodic retesting. Multiple assessment metrics would capture data at the beginning and end of the 2-week in-lab TLNS intervention period and at 3-week intervals. sMRI was performed before the first intervention ('pre') and then 4–6 hours after the training session ('post') of the TLNS intervention. Overall, five patients received HFP and four patients received LFP stimulation.

Behavioural Testing

SOT is an objective, automated measure of sensory-motor integration that evaluates the functional contribution of the somatosensory, visual, and vestibular components of balance. All participants were tested SOT on the NeuroCom® Computerized Dynamic Posturography (CDP) before and after the week of twice-daily interventions.

Dynamic Gait Index (DGI) is a clinician-scored index of 8 facets of gait. Scores range from 0 (worst) to 24 (normal). A score change of 3.0 is generally considered clinically significant. The DGI scores indicate significant improvements in stability and gait that are retained for as much as

6 hours after completion of the second intervention session in the day.

MRI Acquisition

sMRI scan (3T MRI GE750 scanner, GE Healthcare, Waukesha, Wisconsin, USA) was performed before the intervention, and was also performed immediately after the intervention. T1-weighted axial anatomical scans were acquired using 3D fast spoiled gradient echo recalled brain volume (FSPGR BRAVO) sequence (repetition time: 8.132 ms; echo time: 3.18 ms; time of inversion: 450 ms) over a 256 x 256 matrix and 156 slices (flip angle: 12°; field of view: 25.6 cm; slice thickness: 1 mm). During the scanning, patients laid supine on the scanner bed and were instructed to close their eyes and keep their heads still to relax.

Data Preprocessing and Statistical Analysis

The preprocessing and statistical analysis for GMV was applied through the toolbox of the CAT12[21] that works together with Statistical Parametric Mapping (version 12, Wellcome Trust Centre for Neuroimaging, London, UK);[22] as well as with MATLAB (MathWorks, Natick, Massachusetts, USA).[23] For the preprocessing, brain tissue was segmented into grey matter, white matter, and cerebrospinal fluid using the segment procedure. Images were transformed nonlinearly to standard stereotaxic space (Montreal Neurological Institute, Montreal, Canada) and resliced to 1.5 × 1.5 × 1.5 mm using the diffeomorphic registration algorithm (DARTEL).[24-27] Grey matter probability maps were then multiplied by the non-linear component of the Jacobian determinant. Finally, modulated grey matter probability maps were spatially smoothed with an 8 mm full-width at half-maximum Gaussian kernel.

For the statistical analysis, the paired t-test (before versus after interventions) was used for calculating the GMV and behaviour score, respectively. The statistical threshold was set to $p<0.05$ and cluster size >212 using the AlphaSim correction[28-30] for GMV, and was set to $p<0.05$ for behaviour score (SOT or DGI in each) with IBM SPSS version 23. Moreover, the correlation analysis between GMV (post- minus pre-) and SOT (or DGI; post- minus pre-) was set to correct $p<0.05$ with IBM SPSS version 23.

RESULTS

There was a significant increase from pre- to post-intervention for both mean SOT ($t_{(8)}$= 2.74; p=0.03) and DGI ($t_{(8)}$= 2.86; p=0.02) based on the paired t-test calculations.

There were also significant changes in GMV in specific brain regions when comparing pre- versus post-treatment (Table 1 and Figure 1). A positive *t*-value represents a decrease in GMV post-, compared to pre-treatment, and the converse is represented by a negative *t*-value.

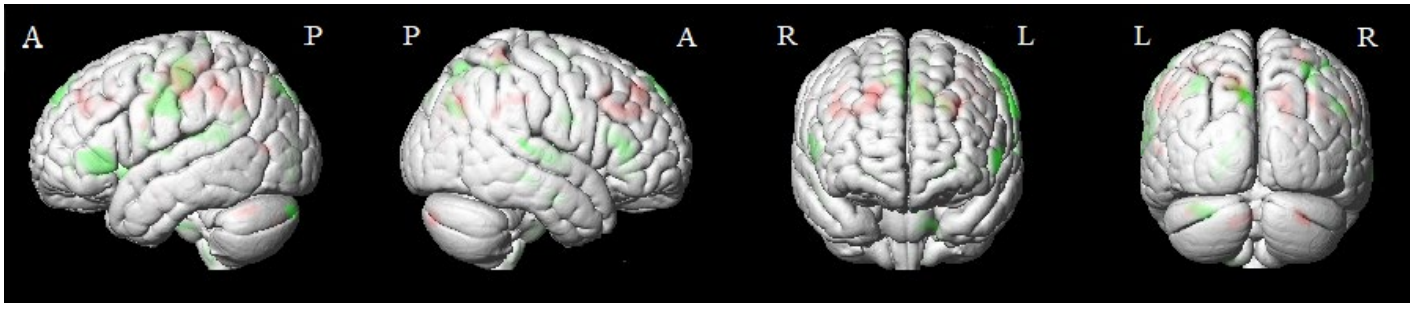

Figure 1: The paired t-test of grey matter volume before (pre-) versus after (post-) treatment. The grey matter volume statistical threshold was used with AlphaSim corrected p<0.05, cluster size >212.

Red: pre- was increased than postintervention.

Negative value: pre- was decreased than postintervention.

Parts of brain: A: anterior; P: posterior; L: left; R: right.

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Table 1: The paired t-test of grey matter volume before (pre-) versus after (post-) treatment.

Brain regions (BA)	Location	Stereotaxic coordinates (Peak MNI Space)			t-value	Number of voxels
		x	Y	z		
Right hemisphere						
Superior frontal gyrus (9)	Frontal lobe	21.0	42.0	40.5	10.21	1,293
Cuneus (7)	Parietal lobe	18.0	-70.5	36.0	16.97	577
Postcentral gyrus (5)	Parietal lobe	28.5	-45.0	64.5	5.65	271
Superior occipital gyrus (19)	Occipital lobe	34.5	-69.0	39.0	22.93	244
Supplementary motor area (6)	Frontal lobe	49.5	-3.0	25.5	-6.06	285
Supplementary motor area (6)	Frontal lobe	13.5	9.0	55.5	-4.16	398
Middle temporal gyrus (21)	Temporal lobe	52.5	-12.0	-24.0	-4.58	253
Superior temporal gyrus (22)	Temporal lobe	60.0	-30.0	10.5	-17.92	853
Left hemisphere (BA)						
Middle frontal gyrus (9)	Frontal lobe	-27.0	39.0	30.0	6.7	379
Superior medial frontal gyrus (32)	Frontal lobe	-6.0	22.5	40.5	9.8	392
Precuneus (7)	Parietal lobe	-6.0	-70.5	40.5	11.76	541
Inferior parietal lobule (40)	Parietal lobe	-61.5	-42.0	39.0	7.47	603
Postcentral gyrus (4)	Parietal lobe	-31.5	-33.0	57.0	11.64	1,759
Superior frontal gyrus (9)	Frontal lobe	-9.0	55.5	42.0	-3.67	561
Postcentral gyrus (6)	Frontal lobe	-63.0	-1.5	33.0	-4.77	718
Pars triangularis (45)	Inferior frontal gyrus	-57.0	33.0	4.5.0	-4.7	1,632
Superior temporal gyrus (22)	Temporal lobe	-63.0	-49.5	19.5	-4.46	213
Superior occipital gyrus (19)	Occipital lobe	-7.5	-87.0	45.0	-9.36	818
Cuneus (18)	Middle occipital gyrus	-12.0	-90.0	13.5	-5.09	278
Cerebellum	Cerebellum posterior lobe	-15.0	-19.5	-45.0	-24.71	438

The grey matter volume statistical threshold was used with AlphaSim corrected p <0.05, cluster size >212.
Positive value: pre- was increased than postintervention.
Negative value: pre- was decreased than post-intervention.
BA: Brodmann area; MNI: Montreal Neurological Institute.

Compared to pre-, post-treatment there were decreases in GMV in nine specific regions (eight of these in the frontal and parietal lobes) and increases across 11 regions of the temporal, frontal, and occipital lobes and cerebellum. A second analysis, employing a Gaussian random field correction, had the same trend for increases and decreases in GMV in the regions noted above.

There were some significant negative correlations between GMV and SOT or DGI (post- minus pre-intervention). The SOT showed all negative correlations to the frontal regions, and the DGI showed all negative correlations to the frontal (right superior frontal gyrus, left superior medial frontal gyrus) and occipital (right cuneus) regions (Table 2). However, no positive correlations were observed between GMV and either SOT or DGI.

DISCUSSION

This substudy of a randomised controlled clinical trial reports notable differences in brain structure in mmTBI patients after TLNS treatment.

Table 2: Correlations between grey matter volume (post- minus pre-) and behaviour testing (post- minus pre-).

	Brain regions (BA)	$r_{(9)}$	p
SOT			
	Right superior frontal gyrus	-0.67	0.05
	Right supplementary motor area	-0.67	0.05
	Right supplementary motor area	-0.68	0.04
	Left superior medial frontal gyrus	-0.72	0.03
DGI			
	Right superior frontal gyrus	-0.69	0.04
	Right cuneus	-0.66	0.05
	Left superior medial frontal gyrus	-0.64	0.06

The statistical threshold was set to corrected p<0.05 with SPSS16.0.

The authors observed that there were increases of brain volumes within the temporal, frontal, and occipital lobes, as well as decreases in volumes within the frontal and parietal lobes, and statistically significant improvements in SOT and DGI assessments post- versus pretreatment. Specifically, the cerebellum had the largest increase in GMV (*t*= -24.71) after therapeutic intervention. The cerebellum is an important junction in the control of balance, because it coordinates information from the vestibular system, the cerebral cortex, and muscles and joints, in order to aid body adjustments and control balance.[31] The second highest increase in GMV was in the right superior temporal gyrus (*t*= -17.92), where activation during balance exercises has been previously reported[32] and may relate to the role of this region in visual–motion processing.

A decrease in GMV after treatment was calculated for several regions, including those associated with sensorimotor processing, visual processing, motor imagery, working memory, and executive function (i.e., right superior frontal gyrus, right cuneus, and left precuneus),[33-36] with the largest decrease observed in the right superior occipital gyrus which is responsible for visual attention[37] or control monitoring.[38] The superior medial frontal cortex also had a decrease in GMV after treatment; this region has the higher-level cognitive functions such as attention, working memory, and cognitive monitoring,[39] and is also involved in automatic subconscious[40] and involuntary motor control.[41] These defined decreases in GMV indicate a degree of structural control and change, after treatment, in brain regions involved in less conscious/automatic motor plans.

Correlative analyses between the GMV and SOT or DGI determined that all changes in GMV were negatively correlated to each assessment; therefore, higher improvements in behaviour score would be associated with less change in GMV in the areas assessed. As mentioned above, the superior frontal gyrus, superior medial frontal gyrus, supplementary motor area, and cuneus are responsible for sensorimotor processing, behavioural control or monitoring, and visual processing, and the negative correlations between the behaviour measure and brain GMV possibly reflect greater efficiency and automatised sensorimotor function after treatment. Moreover, it is speculated that in addition to the brain regions listed in Table 2, the more improved score on behavioural assessment possibly indicates the more other potential regions are involved to play the compensatory role in participants with TLNS treatment. In other words, the improved score on behaviour assessment could reflect adaptive plasticity of functional or structural connections among brain regions, which is a result of brain recovery.[42]

While these initial results are compelling, the small sample size of this substudy does impose two basic limitations of the analyses that should be further investigated with follow-up studies with more patients. First, many of the less significant regions (*t*-value <10) in GMV should be further investigated with a larger patient population to determine if a larger sample size will produce similar outcomes. Additional analyses will help support the purpose of this pilot study, which was to demonstrate, preclinically, the significance of the efficacy of TLNS stimulation to treat mmTBI. Secondly, the HFP and LFP groups were pooled for outcomes analyses; their separation will more specifically define recovery outcomes provided by the HFP device.

The adverse effects of the TLNS treatment should also be noted. The sensation during stimulation could become uncomfortable at high intensity levels, which could be distressing to the participants. In pilot studies, some participants had reported a mild tingling sensation that lasted from several minutes up to an hour after the stimulus was turned off.[13] Although this sensation might feel unusual, it was not reported to be annoying and did not interfere with normal activities, because participants could preset the intensity level to within the preferred stimulus intensity range, between sensation threshold and maximum level without discomfort.[13] The current study also confirmed this. Moreover, participants might experience excess salivation as a result of the presence of the PoNS in mouth, and because more than one participant would use the same device there was a potential for disease transmission. This risk was reduced to an extremely small level by three mechanisms: first, participants typically learnt to regulate saliva by learning to swallow with the device in their mouth, so this way was less a risk than a side effect; second, participants reporting transmittable diseases, or having apparent oral lesions or inflammation, would not be allowed to participate in the study; third, the electrode array would also be cold sterilised according to the protocol developed and approved by the Infection Control Office at University of Wisconsin Health Center. Furthermore, participants would be performing balance and gait tasks that might cause them to lose their balance or fall, so they were protected wherever possible. During in-lab balance training, the participants were surrounded on three sides by a custom laboratory bench designed for this purpose, while the treadmill had a handrail that surrounds the participant on three sides. Additionally, participants might be required to wear a safety belt during gait tests and training to prevent falls.

SUMMARY

Overall, these results suggest that patients may demonstrate improvements in balance and movement with increase in involvement of the neural regions involved in automatic subconscious[40] and involuntary motor control, gait, and balance[41] and decrease in involvement of neural regions involvement in planning, visual, executive function, or cognitive functions. Although additional information can be gained in follow-up studies, this current substudy indicated that TLNS is a safe, effective, and integrative method to treat mmTBI. The benefits from this intervention include symptom improvement that will affect the patients' quality of life and functional capacities. These benefits far outweigh the risks associated with the study. With proper instruction and monitoring, these risks could be managed and minimised and could also improve the rehabilitation outcomes of people with chronic symptoms experienced with TBI.

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Abdominal Textiloma Mimicking as Left Colic Tumour: A Postoperative Complication Still Common in Low-Income Countries

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Abstract

Retained foreign bodies have become very rare in countries where the safety rules in the operating theatre are very rigorous and follow precise guidelines. There are low-income countries where hospital structures are precarious, in which the implementation of surgical safety rules has only been effective recently. Surgical teams in these countries are not yet well trained in the observance of the guidelines concerning swab count, meaning that textilomas are not uncommon. Abdominal textiloma may be asymptomatic, or present serious gastrointestinal complications such as bowel obstruction, perforation, or fistula formation because of misdiagnosis. It may mimic abscess formation in the early stage or soft tissue masses in the chronic stage. This case report presents a 27-year-old female who underwent an emergency laparotomy in a rural surgical centre for an ectopic pregnancy. Two months later, a swelling had appeared on the left side of her abdomen, gradually increasing in size, which was not very painful but caused digestive discomfort and asthenia. Intermittent fever was described and treated with antibiotics. The patient was referred to a better equipped centre to benefit from a CT scan. A textiloma was strongly suspected on the CT but a left colic mass was not excluded. Laparotomy confirmed the diagnosis of textiloma and the postoperative course was uneventful. Prevention rules must be strengthened in these countries where patients can hardly bear the costs of iterative surgeries for complications that are avoidable.

INTRODUCTION

Despite the establishment of sponge count during the operative checklist, foreign bodies such as surgical gauze can be left behind. The exact incidence of intra-abdominal foreign bodies is not known because of under-reporting or unrecognition.[1] In June 2015, 205 articles

on textilomas were collected by Mercier et al.[2] Depending on location within the peritoneal space, clinical symptomatology may vary from mild abdominal pain to serious complications such as bowel or visceral perforation, obstruction, fistula formation, or sepsis.[3] The imaging appearance of textilomas is not widely known and they can be mistaken for a soft tissue tumour.[4] In Madagascar, textiloma incidents are not uncommon. Operative checklists in operating theatres have only become systematic very recently. Given the poor working conditions and the lack of staff in the context of emergency surgery, some surgical teams do not follow the mandatory steps recommended by the guidelines from the Association of Perioperative Registered Nurses (AORN) regarding swab count.[5]

The authors describe a case of intra-abdominal textiloma mimicking a left colonic tumour, which appeared 2 months after an emergency laparotomy for ectopic pregnancy. The first operation was carried out in a rural surgical centre. Throughout the description of this case, a review of the literature concerning variations in the clinical and radiological presentation of textilomas is made. The authors would also like to emphasise the importance of swab counting, as per the guidelines, especially in low-income countries.

CASE REPORT

A 27-year-old female patient was referred to a visceral surgery ward in October 2018 because of abdominal swelling localised in the left quadrant of the abdomen, near the umbilicus. Two months previously, the patient had undergone an emergency laparotomy for ectopic pregnancy and became aware of a palpable abdominal mass on the left side of the abdomen, which become painful 1 month after an uneventful postoperative course. The mass increased in size and was associated with pain and intermittent fever. The patient also presented with asthenia, anorexia, and food vomiting in the late postprandial period, with moderate weight loss. There was no sign of intestinal obstruction and the patient was given oral painkillers and antibiotics each time she had a fever. No blood tests or imaging were performed to explore this postoperative mass in the hospital where the previous surgery was carried out. Because of the persistence of symptoms and a progressive deterioration of her general condition, the patient decided to seek an alternative centre for treatment. Physical examination revealed asymmetry of the abdomen with the left side being deformed by swelling. Inspection of the abdomen showed that the previous surgical approach was a transverse Pfannenstiel incision.

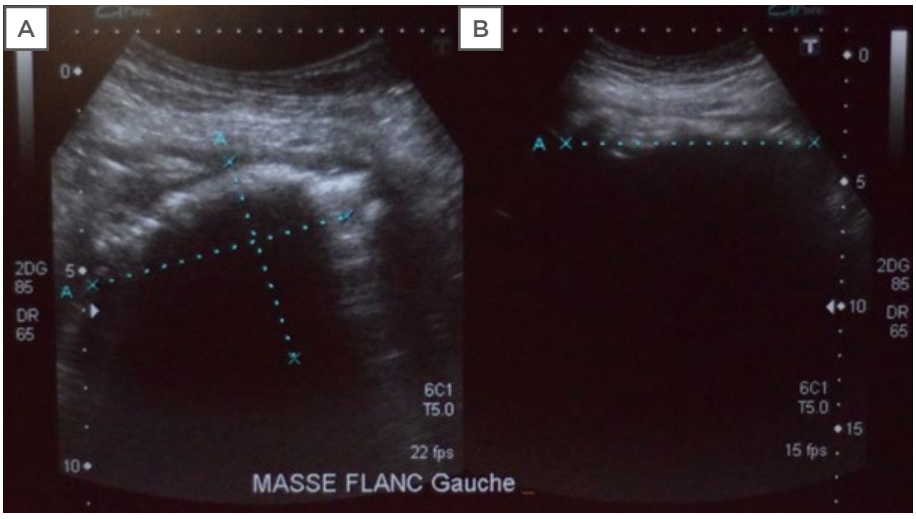

Figure 1: A) Axial and B) ultrasound sections showing an intraperitoneal, hyperechoic mass under the left hypochondrium with a posterior shadow cone.

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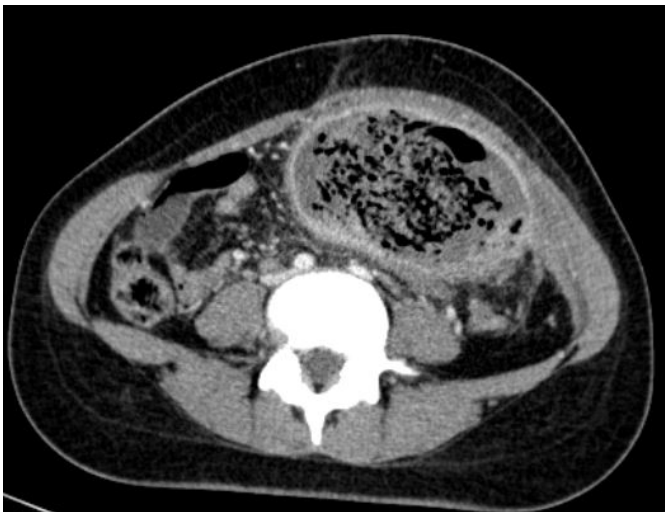

Figure 2: CT with intravenous contrast injection axial cut. Intraperitoneal heterogeneous hyperdense formation under the left hypochondrium with mixed component that did not enhance with intravenous contrast injection.

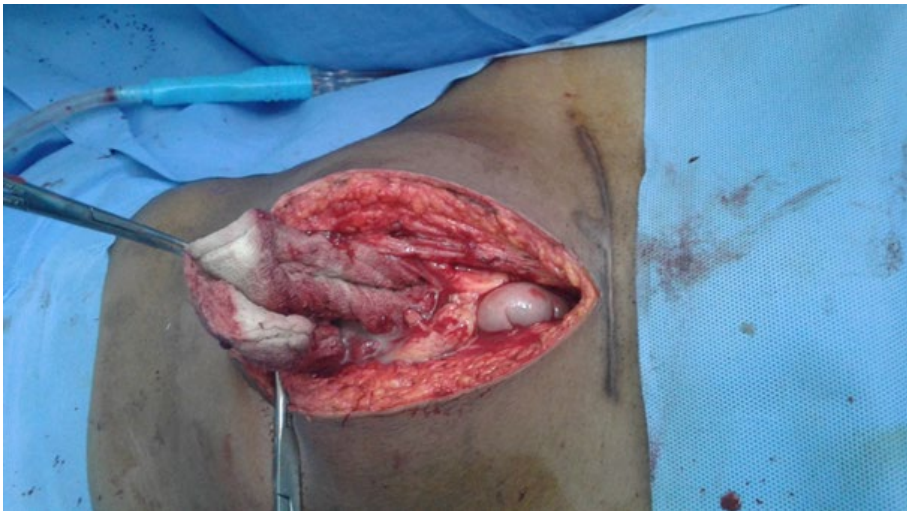

Figure 3: Opening of the mass with evacuation of purulent fluid, allowing extraction of a gauze sponge foreign body inadvertently left at the time of a previous surgical procedure, performed with a transverse Pfannenstiel incision.

The earlier operation was performed at another hospital and it was difficult to obtain sufficient information about the surgical procedure from the patient.

There was a marked tenderness in the whole abdomen. The day she arrived in the centre, she no longer had a fever. White blood cells were moderately raised to 12,000 /mm^3. A plain film of the abdomen showed limited opacity in the projection of the left flank, with air-fluid levels wider than the height of the projection of the hypogastrium. The abdominal ultrasound revealed a large mass at the left flank and a heterogeneous hyperechoic echostructure centred by gaseous structures with posterior shadow cones which measured up to 9 cm long, surrounded by infiltrated bowel (Figure 1). CT showed a left paracolic, well delineated, spontaneously hyperdense mass, which was not enhanced after injection of intravenous contrast. There was a fluid collection mixed with stercoral materials, with air-fluid level mimicking abscess formation inside a tumoural colonic mass adjacent to the left anterior abdominal wall (Figure 2). The descending and sigmoid colon were infiltrated

with parietal thickening, associated with a low abundance of intraperitoneal liquid effusion. Gossypiboma was considered because of the recent surgical history, but a locally advanced colonic left tumour was not excluded because of the stercoral materials inside the mass. At laparotomy, a fluid containing mass adherent to the abdominal wall, strongly encrusted inside the sigmoid colon, was excised. After evacuation of approximately 400 mL of purulent fluid, a surgical sponge was successfully extracted (Figure 3), leaving a perforated colon on the anterior side. Abundant washing was performed. Because of the sepsis of the operative site, immediate end-to-end anastomosis of the colon was contraindicated. A temporary colostomy was made and the postoperative course was unremarkable; the patient was discharged on the seventh postoperative day.

DISCUSSION

Textiloma and gossypiboma are technical terms used to describe a mass of cotton matrix that is left behind in a body cavity during an operation. The term 'gossypiboma' is derived from the Latin word gossypium, meaning cotton, and the Swahili word boma, meaning place of concealment.[6] The first case of a gossypiboma was reported by Wilson in 1884.[7] Areas of location within the body are variable. Although the most common site reported is the abdominal cavity, almost any cavity or surgical procedure may be involved. Other sites reported are the nose, tracheobronchial tree, breast, pancreas, pararenal space, vagina, femur, and spine.[8,9]

In 2015, Arikan and Kocakusa[10] described 14 textiloma cases, whose treatment procedures had been followed-up personally by them over a period of 27 years, almost the whole of their professional lives.[10] Locations of textilomas in the patients included the abdominal cavity in seven cases, inguinal surgical wound in four, epigastric surgical wound in one, thyroidectomy lodge in one, and bilateral axillary cavities in one. The case reported here is one of the most commonly seen since it is an intra-abdominal textiloma in a Malagasy woman. The last case of textiloma reported by the Malagasy authors dates from 2017.[11] Cases of textiloma are not rare in Malagasy hospitals, but the cases reported are still few. In low-resource countries, poor working conditions and non-observance of universal precaution, risk factors for the occurrence of textiloma, prevail in the operating theatre. In Madagascar before 2015 swab count was not performed systematically, but according to the surgeon's habits, however, all surgeons regardless of the socio-economic context of their place of practice should be aware of the importance of the guidelines regarding swab count in the operating room. Despite good performance of the counting protocols, incidents of retained sponges and instruments can sometimes occur.

With regard to clinical presentations and complaints, most intra-abdominal foreign bodies remain asymptomatic, and can be detected incidentally after many years. Adhesions and encapsulation are common features of gossypiboma and the lesion may present as a mass.[12] Similarly, textiloma of the patient in this report was detected as a solid appearance at clinical examination and on CT 2 months after the initial surgery. Atay et al.[12] described the case of a 50-year-old female patient, previously operated on because of a pelvic pleomorphic sarcoma in an outside centre 3 months before admission.[12] The textiloma was initially taken as a tumour recurrence in the case described by this author. In a paper published by Arikan and Kocakusak,[10] reporting on 14 textiloma cases in a period of 27 years, the mean time interval until diagnosis was 14.48 (median: 5.50) months. Some authors have reported cases discovered several years after the initial surgery. The case of a 64-year-old female with a foreign body retained in the liver 39 years after a perihepatic gauze packing described by Xu et al.[13] represents the longest time for which a foreign body has been retained in the liver. Another Malagasy case concerning a 39-year-old female patient who underwent subtotal hysterectomy 7 years previously was described by Rasoaherinomenjanahary et al.[11]

The diagnosis of gossypiboma can be difficult because it can mimic a benign or malignant soft tissue tumour in the abdomen and pelvis.[14] In this case, the patient noticed an asymmetry in her abdomen 1 month after the surgery, caused by the mass, which gradually increased in size, raising doubts between an advanced colonic tumour or a textiloma. The absence of this mass before the operation suggested an iatrogenic cause rather than a tumour. While the gossypiboma

remains in the body, extrusion of the gauze can occur externally through a fistulous track or internally into the rectum, vagina, bladder, or intestinal lumen.[15] Either by fistulising to a lumen or through direct migration, it can cause intestinal obstruction, malabsorption, and gastrointestinal haemorrhage.[16] In this case, the postoperative foreign body became embedded in the left colic lumen, creating a fistula between the anterior side of the sigmoid colon and the capsule enveloping the textiloma. Fistulisation explains the absence of signs of intestinal obstruction in the present case. This situation, already suspected by the CT, was confirmed intraoperatively when the extraction of the textiloma left a perforation of the underlying sigmoid colon.

Many characteristic radiological findings can be used to diagnose gossypiboma. Radiographs are the most commonly used method to detect retained sponges.[17] If the sponge contains a radiopaque marker, the diagnosis can be made easily using conventional radiography.[17-19] Radiolucent material such as sponges can cause diagnostic problems. For this patient a plain film of the abdomen was performed, but it was not contributive because the retained foreign body was not radiopaque and the diagnosis was uncertain. This diagnostic doubt led to an abdominal ultrasound and a CT scan. Ultrasound is useful in the diagnosis of abdominal retained gauze. Ultrasound features are usually a well delineated mass containing a wavy internal echo with a hypoechoic ring and strong posterior acoustic shadowing.[20] These ultrasound signs were found in the case described here. CT is the technique of choice for detecting gossypibomas and possible complications. Many authors consider a gossypiboma to be specifically indicated by a CT finding of a low-density heterogeneous mass with an external high-density wall that is further highlighted on contrast-enhanced imaging and that has a spongiform pattern containing air bubbles.[17-19,21] In this case, the CT confirmed the diagnosis by showing a very limited mass with mixed content, very characteristic of a postoperative foreign body.

Yuh-Feng et al.[22] reported the 18F-fluorodeoxyglucose PET with CT (18F-FDG PET/CT) findings of an intra-abdominal gossypiboma in a 42-year-old woman who had undergone caesarean section twice previously. To date, only a few reports of the MRI appearance of gossypiboma in the abdomen and pelvis have been published. In the case reported by Atay et al.[12] about textiloma mimicking tumour recurrence, CT was completed by MRI because of the difficulties with the diagnosis. The patient in this case report could not benefit from these two imaging exams due to their unavailability in the hospital centre; however, CT was sufficient to make the diagnosis of textiloma. This is in agreement with the data already published by several authors on the contribution of CT in the diagnosis of retained foreign bodies.[17-19,21]

Exploratory laparotomies, emergency, and complex surgeries performed in unstable patients, with unplanned changes in the surgical procedure, needing haemostatic textiles and, often, performed by tired medical teams in improper environments, are the main risk factors for retained foreign bodies during surgery. In the study by Cima et al.,[23] the majority of retained bodies occurred in routine and elective open surgeries. The patient in this case report underwent an emergency surgery for acute abdominal pain due to an ectopic pregnancy and transversal Pfannenstiel incision was performed. The site of the textiloma suggests that it was used to achieve haemostasis and to push back the intra-abdominal viscera in order to facilitate the exposition. Brazilian authors have also experienced the same situation, reporting that during emergency surgeries, sponges are routinely inserted into cavities to expose the operative field. The transverse incision during the previous surgical procedure in the case of this patient, may have contributed to the occurrence of this incident. The surgical sponge had probably been placed deep in the abdomen, far from the surgeon's field of vision, and mixed with blood at the end of the procedure. According to the guidelines from AORN regarding swab count,[5] sponges should be counted during all procedures in which the possibility exists that a sponge could be retained in the patient. Sponge counts should be performed before the procedure to establish a baseline, before closure of a cavity within a cavity, before wound closure begins, at skin closure or end of the procedure, and at the time of permanent relief of either the scrub person or the circulating nurse.

Patient safety rules in the operating room have been in effect for decades in high-income countries whereas in low-resource countries, as is the case here, the application of these rules is recent. Most of the surgical centres far from the city have not yet received adequate training on recommended practice for sponge, sharps, and instrument counts. Therefore, some teams still have trouble achieving the required safety standards. However, even in teams already trained, retained foreign bodies can occur despite rigorous precautions. Greenberg et al.[24] reported the frequency and significance of discrepancies in the surgical count; in a prospective study, they evaluated the rate and type of discrepancies encountered. The authors concluded that one in eight surgical cases involves an intraoperative discrepancy in the count. The majority of these discrepancies detected unaccounted-for sponges and instruments, which represents potential retained sponges and instruments.[24]

One author reported that small aesthetic incisions can contribute to retained foreign bodies during a surgical procedure.[25] In the case described here, the surgeon who performed the first operation opted for a transverse incision for aesthetic purposes. However, procuring aesthetics was a source of exposure problems during the operation. Added to this was the unavailability of radiopaque sponges in these distant surgical centres, as well as the below-standard working conditions usually experienced in operating theatres in low-resource countries. A gossypiboma should be removed using an appropriate intervention such as open or laparoscopic surgery as well as by endoscopy, in which intraluminal cases are detected, in accordance with different parameters of the textiloma such as its duration in the body, localisation, and the clinical condition it had developed. Rarely, a spontaneous discharge of the foreign body by the rectal route has also been reported.[26] When an intracorporeal mass is observed, surgeons should elaborately investigate the patient's past surgical history by considering the possibility of a textiloma because they are able to mimic any malignant condition.[10]

Reintervention through open surgery is the best therapeutic choice to remove gossypiboma as soon as the diagnosis is suspected, and this is what the authors of this case did. Indeed, these postoperative foreign bodies are often extracted under septic conditions making an open laparotomy more justified than a laparoscopic approach to the extraction.

Gossypibomas are in fact preventable burdens which create very severe problems for both patients and surgeons, making their prevention far more important than their cure. Careful counting of the gauzes and surgical towels both before and after any major or even minor surgical interventions, re-exploration of the surgical site in cases of any conflict of counting, usage of the routine postoperative plain X-ray imaging to detect any incidental case if gauzes are labelled preoperatively, and usage of gauzes and towels with long tails which stay extracorporeally during the operation are preventive measures to minimise the problem, although human-based errors cannot be totally abolished.[10] In some institutions, radiofrequency scanning for electronically tagged surgical sponges has been introduced for all operative cases as an addition to standard counting procedures to check for retained sponges.[25] However, in a low-resource country, as it is the case here, such costly paraclinical investigations are not yet available and primary prevention remains the rule. In this case, the patient had to accept all costs related to the two operations. Added to this is the cost of travelling to receive treatment in a better-equipped centre in the capital, and the cost of the CT. Subjecting a patient to a second operation because of an iatrogenic, yet avoidable, complication is unacceptable. Such complications should no longer occur in the present day.

CONCLUSION

Textilomas occur mostly in routine procedures, mainly in laparotomies and at the beginning of the professional career, highlighting, particularly in low-income countries, the need for primary prevention. Given the resource-limited conditions of many African hospitals, it is essential to minimise preventable surgical complications such as textilomas through high-quality training about safety rules during surgery. Challenging medical situations, omission of security protocols, and inadequate work conditions contribute to postoperative retention of foreign bodies. The context of developing countries does not excuse a lack of rigor and meticulousness in respecting safety rules in the operating theatre.

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The Value of Endometrial Volume as Estimated by Three-Dimensional Ultrasound for Detecting Endometrial Cancer in Postmenopausal Women: A Systematic Review and Meta-Analysis

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Abstract

Objective: To analyse the diagnostic performance of endometrial volume calculated by three-dimensional (3D) ultrasound for diagnosing endometrial carcinoma in women with postmenopausal bleeding.

Methods: An extensive search of papers analysing the role of endometrial volume calculated by 3D ultrasound for diagnosing endometrial carcinoma in women with postmenopausal bleeding was performed in MEDLINE/PubMed and Web of Science from January 1996 to January 2020. Quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool.

Results: The extended search identified 318 citations but after exclusions, eight articles were included in the meta-analysis. The risk of bias for most studies was high for the four domains assessed in QUADAS-2. Overall, after excluding three studies that contributed significantly to heterogeneity, pooled estimated sensitivity and specificity for diagnosing endometrial cancer were 87% (95% confidence interval: 80–92%) and 60% (95% confidence interval: 51–68%), respectively. Heterogeneity was low or moderate.

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Conclusion: Endometrial volume as estimated by 3D ultrasound using virtual organ computer-aided analysis (VOCAL™) software has a moderate diagnostic performance for detecting endometrial malignancy in women with postmenopausal bleeding.

INTRODUCTION

Endometrial carcinoma is the most frequent gynaecological malignancy in western countries, with most of the patients being postmenopausal.[1] The main symptom of this disease is postmenopausal bleeding. The first approach to take in a woman who is symptomatic is to evaluate the endometrial thickness using two-dimensional ultrasound because a endometrial thickness <5 mm has a very high negative-predictive value (99.3%) when ruling out endometrial cancer, meaning that unnecessary biopsies can be avoided.[2] In contrast, a thickened endometrium (>5mm) is a relatively nonspecific finding that can be found in many benign endometrial pathologies, such as cyst atrophy, polyp, or non-atypical hyperplasia. In fact, the specificity reported is approximately 50.0%.[2,3]

In the last two decades, three-dimensional (3D) ultrasound has become available for the diagnosis of some gynaecological diseases. Currently, 3D ultrasound is considered the first-line imaging diagnostic technique for some gynaecological lesions, such as congenital uterine anomalies.[4] Furthermore, extensive research using this technique has been reported in the fields of reproductive medicine[5] and gynaecological oncology.[6]

The estimation of endometrial volume using 3D ultrasound is accurate[7] and reproducible among examiners.[8,9] Specifically, the role of the endometrial volume for diagnosing endometrial carcinoma in women with postmenopausal bleeding has been evaluated in a small number of small-scale prospective studies since the first report on its use in 1996.[10] However, the role of this technique as a diagnostic test in this clinical setting has not been clearly established.

The aim of this systematic review and meta-analysis is to evaluate the diagnostic performance of the endometrial volume calculated by 3D ultrasound for diagnosing endometrial carcinoma in symptomatic postmenopausal women.

METHODS

Protocol and Registration

This meta-analysis has been performed according to the PRISMA statement and the Synthesizing Evidence from Diagnostic Accuracy Tests (SEDATE) guidelines.[11] The protocol was not registered, a decision made by the researchers to avoid delays in starting the meta-analysis. All inclusion and exclusion criteria for studies to be selected were defined, as well as how data extraction and quality assessment had to be performed before starting the data search. Because of the study's nature and design, Institutional Review Board (IRB) approval was waived.

Data Sources and Searches

Two of the authors (SC and CM) screened two electronic databases, MEDLINE/PubMed and Web of Science, to identify potentially eligible studies published from January 1996 to January 2020. The search terms included and captured the concepts of "endometrial cancer", "endometrial malignancy", "three-dimensional ultrasound", "postmenopausal bleeding", and "endometrial volume". The language limit was set to English.

Study Selection and Data Collection

Two authors (CM and RD) screened the titles and abstracts identified by the search to exclude irrelevant articles. Then, full-text articles were selected to identify potentially eligible studies by applying set criteria:

- prospective and retrospective cohort studies that included patients with postmenopausal bleeding who underwent transvaginal ultrasonography examinations and included the calculation of endometrial volume using the virtual organ computer-aided analysis (VOCAL™) method;
- histological findings evaluated with endometrial samplings or hysterectomy;
- presence of data reported that would allow construction of a 2×2 table with a specific

cut-off of endometrial volume to estimate the diagnostic accuracy.

To avoid inclusion of duplicate cohorts from at least two studies reported from the same authors, the study period of each study was examined; if dates overlapped, the latest study published was selected. Additional articles were searched by reading the reference lists of those articles selected for full-text reading. The patient, intervention, comparator, outcome, and study design criteria used for inclusion and exclusion of studies were recorded.

The authors had intention to assess data based on individual patient information; therefore, they contacted the authors from the selected studies asking for specific data about some clinical characteristics of the patients, 3D ultrasound endometrial volume estimation results, and histologic data. This way, using the predefined endometrial volume, thresholds reported from the authors in the respective paper could be avoided. However, no responses were received from any of the authors. Therefore, the quantitative analysis using the respective threshold reported in each paper was performed.

Diagnostic accuracy results from the selected studies were retrieved independently by two authors (CM and RD). Disagreements arising during the process of study selection and data extraction were resolved by consensus among all four authors.

Risk of Bias in Individual Studies

A quality assessment of studies included in the meta-analysis was conducted by using the tool provided by the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2).[12] The QUADAS-2 format includes four domains: 1) patient selection; 2) index test; 3) reference standard; and 4) flow and timing. For each domain, the risk of bias and concerns about applicability (the latter not applying to the domain of flow and timing) were analysed and rated as low, high, or unclear risk. The quality assessment was used to provide an evaluation of the overall quality of the studies and to investigate potential sources of heterogeneity.

Three authors (CM, RD, and JLA) evaluated the methodological quality independently. Disagreements were solved by discussion between these authors. The assessment of the quality was based on several issues, depending on the domain assessed. For the patient selection domain, the authors considered whether the study described the study's design (in retrospective studies in which the reference test was already known by the researchers when performing the index test could not be elucidated, the worst case scenario was opted for and these were considered studies with a high risk of bias) as well as patients' inclusion and exclusion criteria. For the index test domain, whether the study reported on the method of 3D volume acquisition and how the volume was calculated was considered, as well as how this was performed and interpreted. For the reference test domain, whether the study reported on the reference standard used (histology or not) and how sample was obtained was considered. Finally, for the flow-and-timing domain, the authors considered whether the study reported on the time elapsed from the index test assessment to the reference test (more than 4 weeks from index test to reference test was considered as high risk for bias).

Statistical Analysis

Information on the diagnostic performance of endometrial volume was extracted. A bivariate model was used to estimate the pooled sensitivity, specificity, positive likelihood ratio (LR), and negative LR. The LR were used to characterise the clinical utility of a test and to estimate the post-test probability of disease.[13] Using 8% prevalence of endometrial cancer in women with postmenopausal bleeding (pretest probability),[2] post-test probabilities were calculated by the positive and negative LR and plotted on a Fagan nomogram.

Heterogeneity for sensitivity and specificity was assessed by the Cochran's Q statistic and the heterogeneity I^2 index.[14] A p value <0.1 indicated heterogeneity, and I^2 values of <25%, 25–50%, and >75% were considered to indicate low, moderate, and high heterogeneity, respectively.

Forest plots of sensitivity and specificity of all studies were plotted. Considering that it could be a threshold effect, given that different studies used different thresholds for endometrial volume, a bivariate random effects modelling of

sensitivity and specificity was used to identify how much the threshold effect could explain heterogeneity, if found.

Hierarchical summary receiver operating characteristic curves were plotted to illustrate the relationship between sensitivity and specificity. Additionally, a binomial exact distribution for assessing within-study variability for sensitivity and specificity was used. Publication bias was assessed by the method of Deeks et al.[15]

All analyses were performed with MIDAS and METANDI commands in Stata version 12.0 software for Windows (StataCorp, College Station, Texas, USA). A p value <0.05 was considered statistically significant.

RESULTS

Search Results

The electronic search provided 318 citations. After exclusion of 120 duplicate records, 198 citations remained. Of these, 166 were excluded because it was clear from the title or abstract that they were not relevant to the review (studies not related to the topic [n=146], reviews [n=9], articles published in non-English languages [n=8], and letters to Editor [n=3]).

The full text of the remaining articles was read. A further 24 studies were excluded: two studies did not use the VOCAL method; 14 studies included only patients with previous diagnosis of carcinoma; four studies included premenopausal and postmenopausal women and data could not be stratified for menopausal status; in three studies it was not possible to retrieve data to make a 2×2 table to calculate true positive, true negative, false positive, and false negative cases; and one study was a retrospective study using the same data of another included study. The remaining eight[16-23] studies were ultimately included in the present meta-analysis. No additional studies from references cited in these eight studies were found.

Characteristics of the Included Studies

Eight studies published between 2007 and 2013 reporting on 981 patients were included in the final analyses. Among these 981 women, 267 had a malignant lesion. The mean prevalence of malignant lesions was 27.2%, ranging from 10.4% to 47.0%. All studies reported some clinical characteristics of the patients. All patients were women with postmenopausal bleeding. Postmenopausal was defined as, at least, 1 year of amenorrhoea in all studies. Pathologic confirmation obtained after endometrial biopsy was reported in all studies.

Methodological Quality of the Included Studies

The study design was clearly stated as prospective in all the studies. The QUADAS-2 assessment of the risk of bias and concerns regarding applicability of the selected studies is shown in Figure 1.

With regard to the risk of bias for the patient selection domain, all studies were considered as having a high risk of bias. Six out of the eight studies included only women with a thickened endometrium, >4 mm;[17-20,22,23] three studies excluded patients with previous gynaecologic disease such as fibroids or polyps;[16,21,23] and one study pooled the hyperplasia with atypia and endometrial cancer in the same group.[16] Concerning the index test domain, all the studies used the VOCAL rotational method to calculate the endometrial volume. In seven studies, the method of the index text as well as how it was performed was adequately described. One study did not describe the angle rotation step used.[22] However, five studies[16,17,19,20,23] were considered at high risk because they used a 30° rotation step for endometrial volume acquisition, and it has been shown that this approach is less reliable than using 9° or 15°.[24,25] Only two studies used less than 30° rotation step, and they were considered as having low risk for bias regarding the index test.[18,21]

For the reference standard domain, all studies were considered low risk because all patients were studied with endometrial sampling and posterior histologic diagnosis. Regarding the flow and timing domain, in four studies the time elapsed between the index test and reference standard was less than 1 week,[17,18,20,23] but in four studies it was unclear.[16,19,21,22]

Concerning applicability, for the patient selection domain, index test, and referent test, all studies were considered low risk for applicability because they used an adequate technique (transvaginal ultrasound) in the adequate clinical setting (postmenopausal bleeding) with an adequate reference standard (endometrial biopsy).

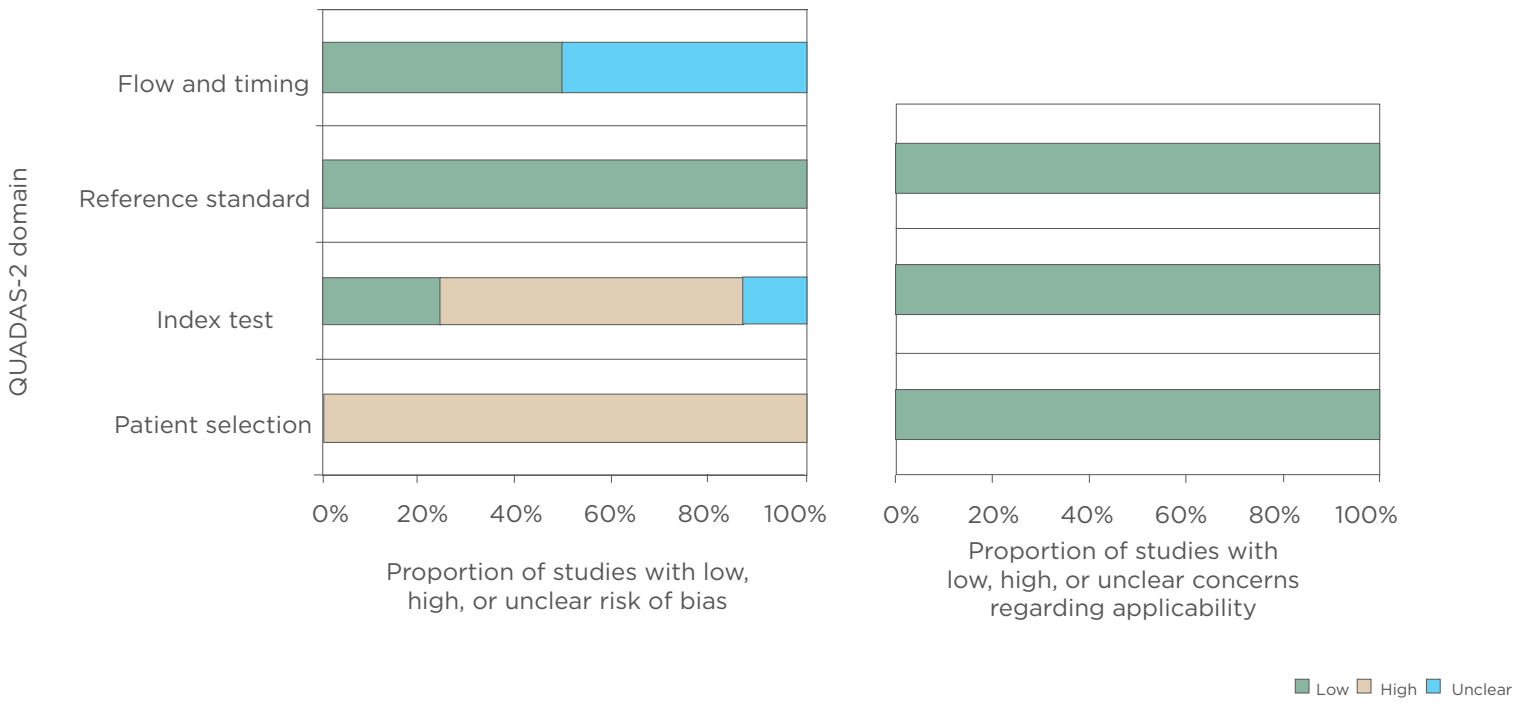

Figure 1: Histogram plot showing quality assessment (risk of bias and concerns about applicability) for all studies included in the meta-analysis.

QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies 2.

Diagnostic Performance of Endometrial Volume for Detection of Endometrial Cancer

The pooled sensitivity, specificity, positive LR, and negative LR of endometrial volume for detecting endometrial cancer were 87% (95% confidence interval [CI]: 77–93%), 69% (95% CI: 54–82%), 2.8 (95% CI: 1.9–4.2), and 0.19 (95% CI: 0.12–0.30), respectively. The diagnostic odds ratio was 15.0 (95% CI: 9.0–24.0). Significant heterogeneity was found for sensitivity (I^2 = 74.48%; Cochran Q = 27.43; p<0.001) and specificity (I^2 = 93.45%; Cochran Q = 106.89; p<0.001). Bivariate modelling showed that a threshold effect explained this heterogeneity with three studies involved.[16,17,19]

After excluding these three studies, pooled sensitivity, specificity, positive LR, and negative LR of endometrial volume for detecting endometrial cancer were 87% (95% CI: 80–92%), 60% (95% CI: 51–68%), 2.2 (95% CI: 1.7–2.7), and 0.22 (95% CI: 0.13–0.36), respectively. The diagnostic odds ratio was 9.9 (95% CI: 5.1–19.3), but no heterogeneity was found for sensitivity and moderate heterogeneity was found for specificity (Figure 2). A hierarchical summary receiver operating characteristic curve for the diagnostic performance of endometrial volume for detecting endometrial malignancy is shown in Figure 3.

The Fagan nomogram shows that an increased endometrial volume increased the pretest probability of endometrial malignancy, from 8% to 16%, whereas a normal finding decreased the pretest probability, from 8% to 2%. No publication bias was observed (p=0.43).

DISCUSSION

Most women with postmenopausal bleeding have a benign aetiology, and fewer than 8-10% will be diagnosed with endometrial cancer.[2,26] Two-dimensional ultrasound is the first step in the evaluation of women with postmenopausal bleeding with the measure of the endometrial thickness because it has been shown to be the most cost-effective strategy in this clinical setting.[27,28]

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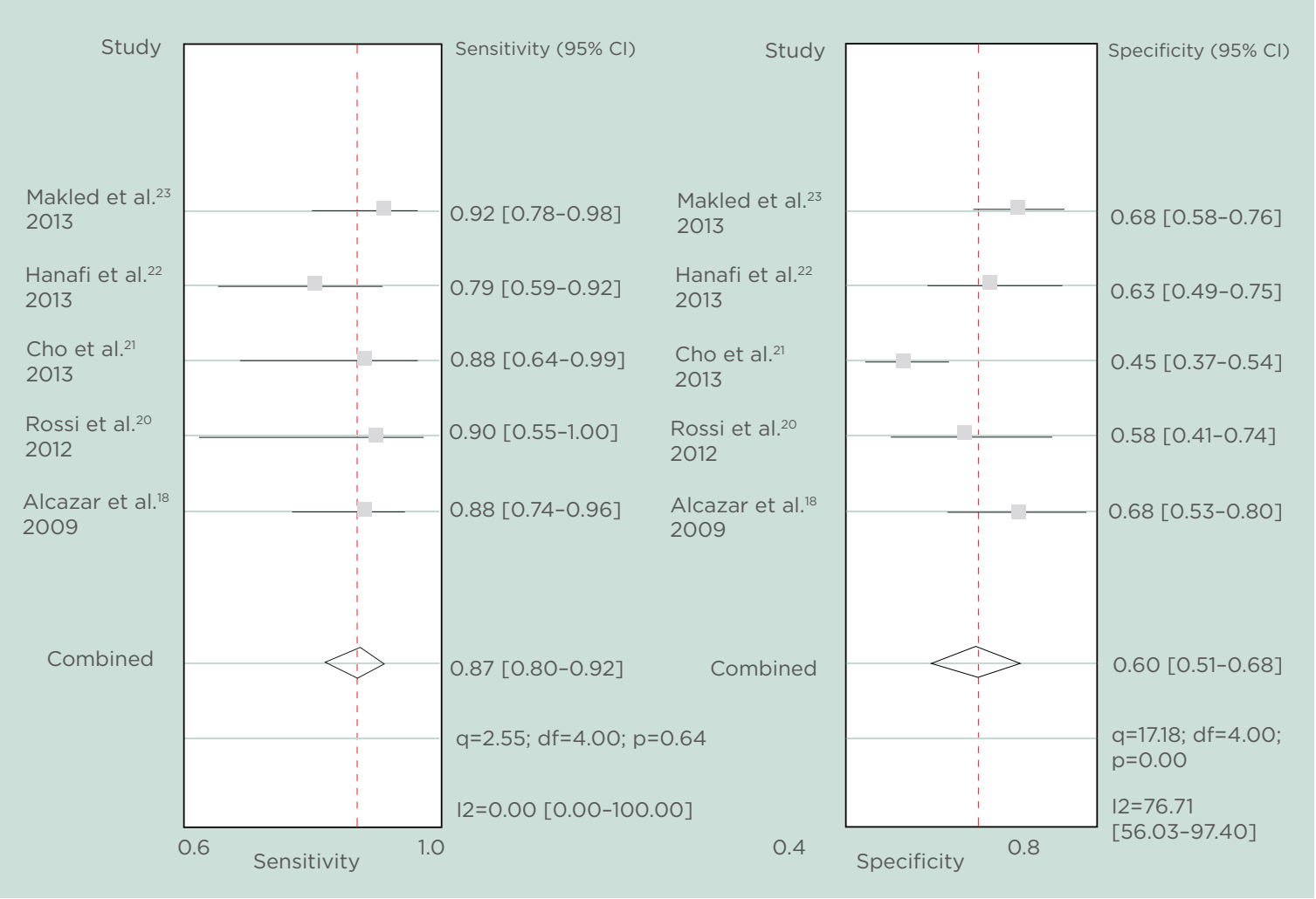

Figure 2: Forest plot for sensitivity and specificity for each study and pooled sensitivity and specificity for endometrial volume, after excluding studies contributing to heterogeneity.

CI: confidence interval; df: degrees of freedom.

Several meta-analyses assessing the diagnostic performance of endometrial thickness for detecting endometrial cancer in women with postmenopausal bleeding,[2,29-32] and even in asymptomatic postmenopausal women,[33,34] have been reported. In women with postmenopausal bleeding, the most recent meta-analysis has demonstrated that an endometrial thickness <5 mm is effective to rule out endometrial cancer, with a high sensitivity (96.2%) and negative predictive value (99.3%), but rather low specificity (51.5%).[2]

The advent of 3D ultrasound allowed an accurate estimation of organ or structure volume.[35] There are different approaches for the estimation of organ volume, such as the use of the prolate ellipsoid measuring the three orthogonal diameters of the structure, using a distance and the perimeter of an ellipse, a spherical method, or the so-called VOCAL method.[35-39] The latter processing system of the 3D volume allows calculation of the volume using a rotational method, with different rotation angles (9°, 15°, 30°).

The assessment of endometrial volume as measured by 3D ultrasound for detecting endometrial cancer in women with postmenopausal bleeding was first reported in 1996.[10] In this study, Gruboeck et al. reported a series of 97 women with postmenopausal bleeding (11 had cancer).

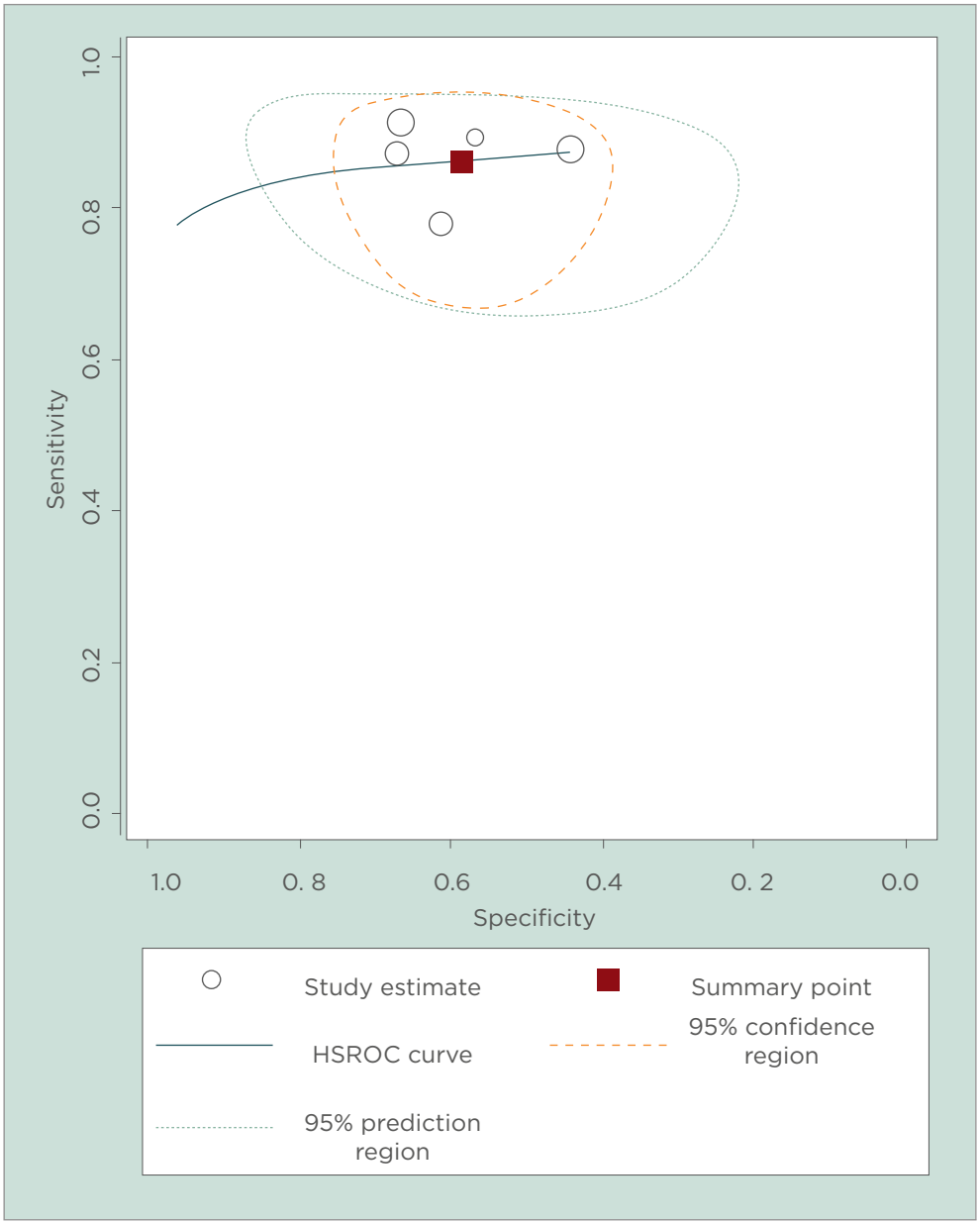

Figure 3: Hierarchical summary receiver operating characteristic curve for endometrial volume.

Area under the curve: 0.87 (95% confidence interval: 0.84–0.90).

HSROC: hierarchical summary receiver operating characteristic.

They showed that an endometrial volume greater than 13 mL had a sensitivity and specificity of 100.0% and 98.8%, respectively, for diagnosing endometrial cancer.[10] However, no further study was reported in the subsequent 10 years. Since 2007, several studies have been published addressing this issue, all of them using the VOCAL method.

In the present meta-analysis, the authors have evaluated the diagnostic performance of endometrial volume as estimated by 3D ultrasound using the VOCAL method to predict the presence of endometrial malignancy in women with postmenopausal bleeding. In the meta-analysis, it was observed that pooled sensitivity and specificity of the endometrial volume were 87% (95% CI: 80–92%) and 60% (95% CI: 51–68%), respectively, after excluding some papers that were identified as potential source of heterogeneity for a threshold effect.

The main strength of this study is that, to the best of the authors' knowledge, this is the first

meta-analysis reported addressing this topic. Long et al.[2] have reported a recent meta-analysis assessing the diagnostic performance of endometrial thickness for detecting endometrial cancer in women with postmenopausal women.[2] In this meta-analysis, four studies were reported on, comprising data from 434 women, analysing 3D endometrial volume in this clinical setting. Out of these four studies, three have been included in this present meta-analysis[18,19,23] and one was not because, from this paper, 2x2 tables could not be extracted.[40] However, they did not perform an analysis about endometrial volume because of the small sample size.

However, the authors do consider there are some limitations that preclude drawing definitive conclusions regarding the role of endometrial volume as estimated by 3D ultrasound to detect endometrial cancer in women with postmenopausal bleeding.

First, the collected sample can be considered as relatively small as compared with that reported on meta-analyses focussed on endometrial thickness. The data presented here are based on 981 women derived from just eight studies, while meta analyses about endometrial thickness report data from 2,896 to 17,339 patients.[29-32]

On the other hand, as stated above, studies that used the VOCAL method for analysing the 3D volumes obtained during the exam, and estimating the endometrial volume, were selected because this method has been reported as the most accurate to estimate the volume of the endometrium.[41] Raine-Fenning et al.[24] described that employing a rotation step of less than 30° was associated with a significantly smaller variance in measurements and a significantly greater mean endometrial volume. In this meta-analysis, most of the studies (in fact, all of them except those from Cho et al.[21] and Alcázar et al.[18]) used a 30° rotation step. This fact could be considered as a source of bias from the technical point of view, since the rotation angle used was not the most optimal for calculating the endometrial volume.

Furthermore, it is important to consider that in six studies the inclusion criteria were only patients with a thickened endometrium, >4 mm, and this also may lead to a selection bias, leaving out from the analysis some cases of endometrial cancer present in symptomatic women with a thin endometrium. It should be borne in mind that 25–34% of the Type II endometrial cancer could be present in patients with thin or indistinct endometrium.[42-43] The authors have no information about endometrial volume in these cases.

In addition, there was high heterogeneity among the studies relating to different cut-off values used for endometrial volume (1.35–5.3 mL). The authors of the papers included were contacted in an attempt to perform a meta-analysis based on individual patient data, but none answered. Therefore, it is difficult to be precise about the specific cut-off value of endometrial volume to rule out endometrial cancer.

In most of the studies, endometrial hyperplasia with or without atypia cases were pooled in the benign group. There were no precise data for differentiating between the hyperplasia with and without atypia using the endometrial volume, so the authors had to be careful in the interpretation of that point, considering that almost 25% of patients with hyperplasia with atypia had a coexistent endometrial cancer in the final histology.[44,45]

Nevertheless, the authors could not compare the diagnostic performance of endometrial volume and endometrial thickness, of which is the current standard.[46-48] Thus, it cannot be elucidated whether endometrial volume is better than endometrial thickness.

CONCLUSION

In conclusion, endometrial volume as estimated by 3D ultrasound using VOCAL software has a moderate diagnostic performance for detecting endometrial malignancy in women with postmenopausal bleeding. A rough comparison with the results from a recent meta-analysis focussed on endometrial thickness suggests that endometrial volume appears inferior to endometrial thickness.[2] However, a formal meta-analytical comparison has not been performed so far. There is clear room for future research in this topic because better-designed prospective studies are needed.

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Two Multiple Sclerosis Relapses Affecting the Left Pontine-Mesencephalic Transition and Later the Right Mid Pons, With Distinct Eye Movement Abnormalities - The Importance Of Semiology Above Medical Imaging: Case Report

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Abstract

The authors report the case of a 22-year-old female patient who presented with two distinct relapses of multiple sclerosis. The first was a lesion in the dorsal paramedian pontine area to the left, and the second, not visible in the MRI but presumably affecting the right medial longitudinal fasciculus, in the pons. In both cases, the semiology was unquestionable and compatible to the proposed areas of demyelination, with the patient fully recovering her eye movements after pulses of methylprednisolone.

INTRODUCTION

Multiple sclerosis (MS) is a demyelinating disorder, in which both humoral and cellular mechanisms of autoimmunity coexist,[1,2] affecting 15 of every 100,000 Brazilians[3] and between <1 and 38 per 100,000 in other regions of Latin America.[4] The majority of patients are white females >30 years of age.[5] Despite constant advancements in research and the development of new medications[6] that have to some extent prolonged survival rate,[7] mortality in the MS population is still around three times higher than the corresponding general population.[8,9]

Cerebellar and/or brainstem lesions in MS happen roughly in one third of the relapses.[10] The authors report a case of two relapses that occurred in a female patient, compatible with demyelination of different areas in the brainstem and displaying a different semiological finding during each relapse.

CASE REPORT

The patient was a 22-year-old woman of mixed black and Brazilian-indigenous background who presented to the emergency department with a complaint of diplopia, numbness in the

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face, and trouble with her balance. During physical examination, she had normal strength (Grade 5) in the face and the four limbs. Cranial nerve analysis showed divergent deviation of the left eye (LE) in the neutral gaze position associated with left hypertropia, a horizontal misalignment of the eyes. Voluntary eye movement tests (Figure 1, Situation 1) displayed a deficit in the adduction (paralysis of the medial rectus) of the LE, with augmentation of hypertropia during dextroversion and limitation of lowering of the same eye during infraversion. Although not doing so unprompted, she reported improvement of her double vision when asked to tilt her head to the right. She did not show ptosis or pupillary changes. Red glass, double Maddox rod, or prisms tests were not performed. Although the presence of paralysis of more than one eye muscle lessens the accuracy of the Parks–Bielschowsky three step test,[11] this was interpreted as a possible left trochlear nerve palsy, in addition to left internuclear ophthalmoplegia.

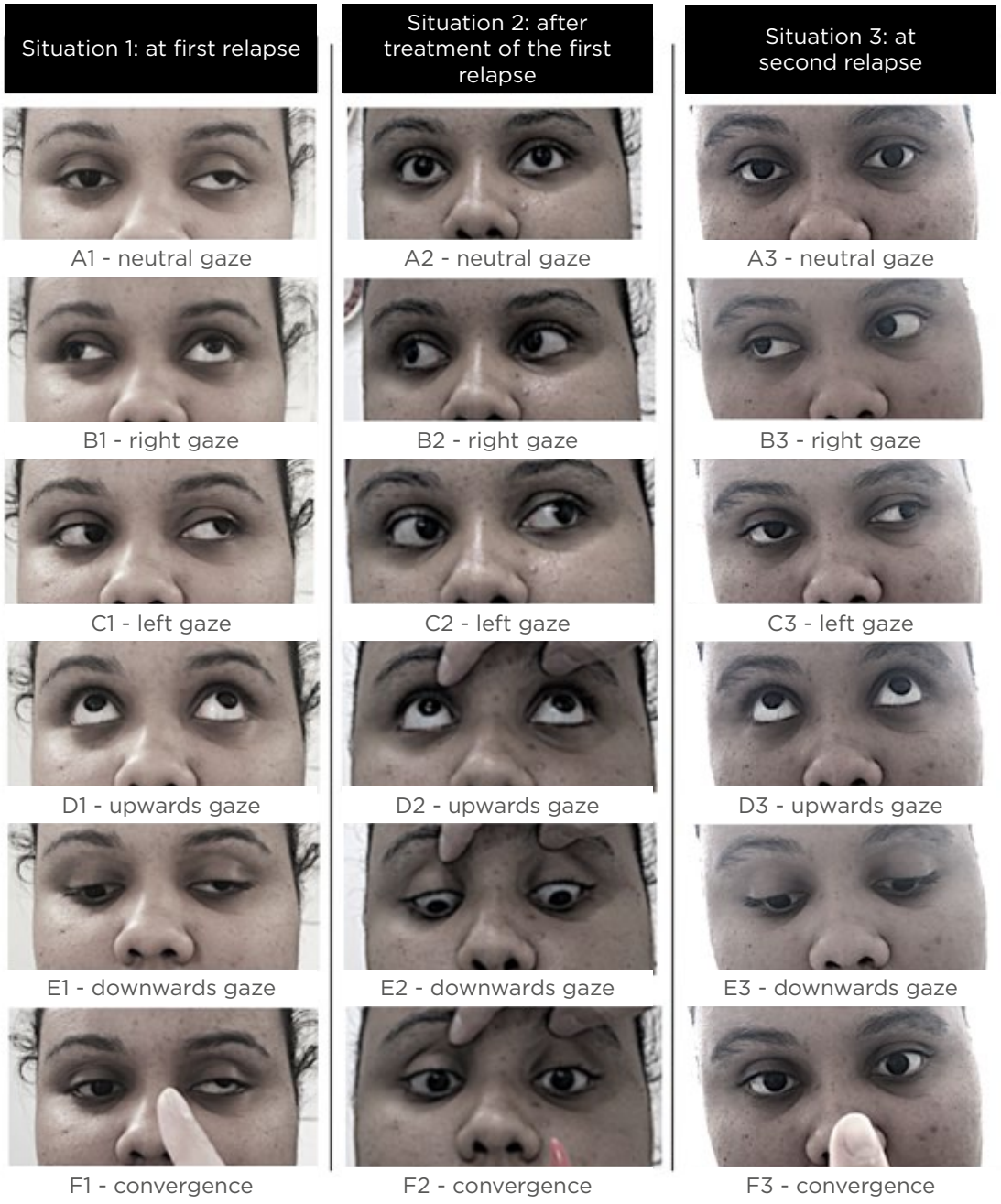

Figure 1: Examination of the eye movements of the same patient for three different situations. Situation 1: at first relapse; Situation 2: after treatment of the first relapse; and Situation 3: at second relapse.

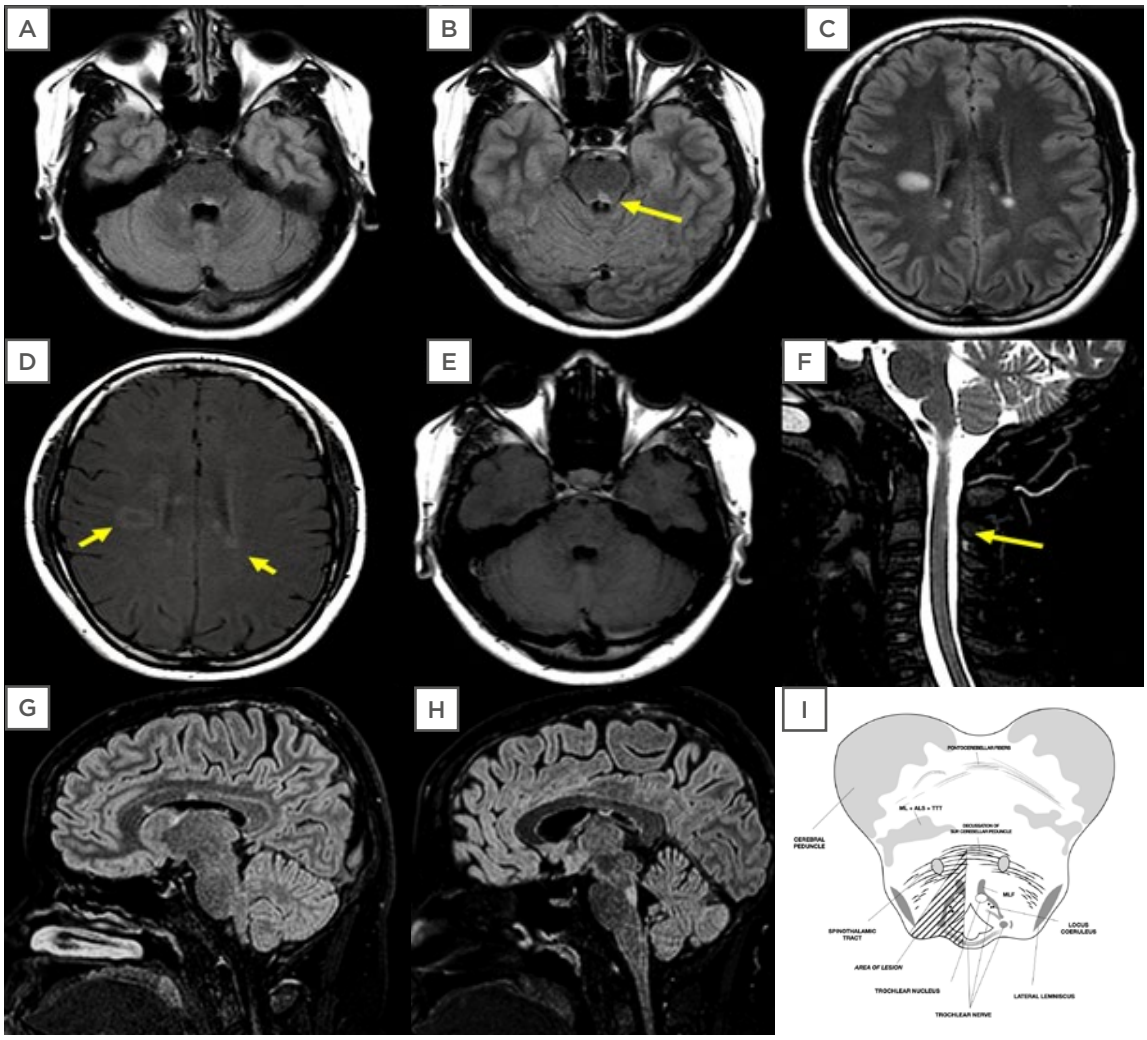

Figure 2: MRI performed at the occasion of the first relapse.

Displayed here are fluid-attenuated inversion recovery sequences (FLAIR) (A, B, C, G, H), T1 with gadolinium (D, E) and T2 acquisitions (F). Supratentorial lesions are visible (C, D, G, H), along with moderate contrast enhancement (D: arrows), which did not happen with infratentorial lesions (A, B, E, G, H) or in the cervical C3 lesion (F: arrow). (I) anatomical representation of the affected area (hatched triangle) of the midbrain pontine transition that is displayed in the arrow in B. The images fulfil radiological criteria for dissemination in time and space, as required in multiple sclerosis.

ALS: anterolateral system; ML: medial lemniscus; MLF: medial longitudinal fasciculus; TTT: trigeminal thalamic tract.

Illustration (I): Adapted from University of Wisconsin-Madison.[13]

Laboratory exams excluded renal, hepatic, rheumatic, or endocrine abnormalities, as well as confirmed negative serology for hepatitis B and C, syphilis, and HIV. Serum levels of vitamin B12 and vitamin D were both within normal range (426 pg/mL and 41 pg/mL, respectively). White blood cell count displayed discrete leukocytosis ($12.3x10^3$ cells/mm^3 [92% segmented cells]), and C-reactive protein levels of 17 mg/L (normal: <10 mg/L), which was attributed to a sinus infection since she also presented with facial pain and purulent nasal discharge. Lumbar puncture revealed 1 leukocyte/mm^3 and protein levels of 22 mg/dL, both within normal value ranges.[12]

MRI of the whole neural axis was performed (Figure 2), showing multiple oval-shaped, hyperintense lesions in T2 and fluid-attenuated inversion recovery sequences in the supratentorial subcortical and periventricular white matter. Some exhibited a perivenular distribution pattern, and others alongside the callosal-septal interface, with contrast enhancement in at least three periventricular lesions and in one lesion

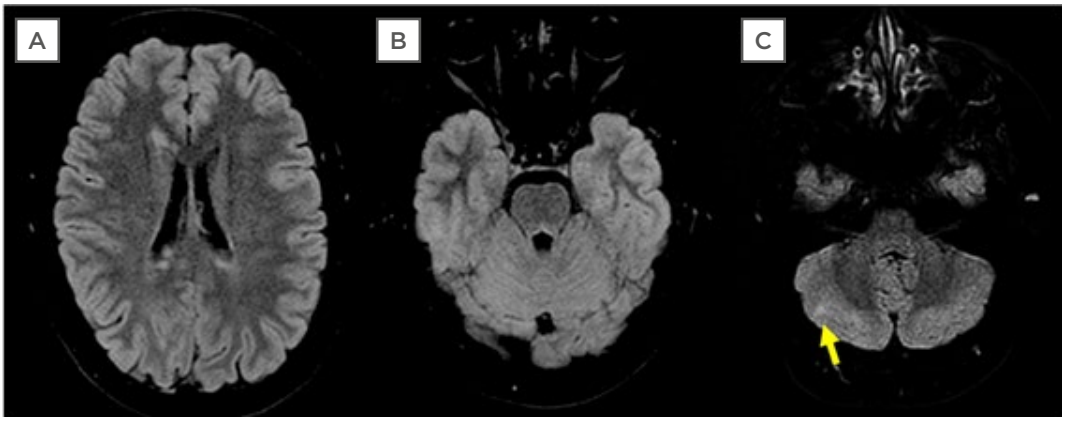

Figure 3: MRI (FLAIR Acquisition) performed by the occasion of the second relapse, 2 months after the first. Although one can see reduction of the prior lesions in A and B, and that no new viewable lesions at the image could explain the clinical exam, which pointed to damage to the right MLF, there is at least one viewable lesion at the cerebellar right hemisphere, indicating that the disease at the moment remained active.

MLF: medial longitudinal fasciculus.

at the right centrum semiovale. There was also another hyperintense, nonenhanced lesion at the posterior medial part of the left pons, extending up to the level of the facial colliculus, which probably resulted in damage to the left trochlear nucleus and the medial longitudinal fasciculus, explaining the findings of the clinical examination. However, by the posterior cervical spine the MRI exposed a hyperintense T2 lesion at C3 level. These aspects fulfilled radiologic criteria for dissemination in space and time of MS.[14]

The patient underwent pulse therapy with intravenous methylprednisolone, the standard treatment for MS relapses,[15] 1 g once daily for 5 days plus antibiotics for the sinus infection, and showed an improvement of ocular movements at discharge, however the complaint of gait impairment was maintained and the patient required a walking cane. One month later, examination in the consultation room revealed normal ocular movements (Figure 1, Situation 2).

Two months after the first admission, the patient developed a new complaint of diplopia. This time, during physical examination, she had a normal range of extrinsic movements of the LE and deficit in the adduction (medial rectum paresis) of the right eye. This suggested a new and different lesion, topographically compatible with a lesion of the right medial longitudinal fasciculus (Figure 1, Situation 3). This time, no hypertropia was present and the eyes were horizontally aligned. Once again, she did not display ptosis nor pupillary changes and this examination was interpreted as a probable right internuclear ophthalmoplegia. A follow-up MRI performed 3 days after the new symptoms onset (and prior to new steroid course) (Figure 3) did not reveal any new lesions in the brainstem, nor any gadolinium enhancement, however there was a small, new lesion at the right cerebellum, suggesting maintenance of the disease activity. Despite the lack of visualisation of the lesion in the expected area, this was interpreted as a new relapse affecting the right pontine area. This was contralateral to the first relapse because the eye movement abnormalities could not be faked, as might be possible in a conversive disorder, therefore demonstrating organicity. Following this, the patient was put on a new regimen of intravenous methylprednisolone (1 g once daily for 5 days) resulting in full ocular movement normalisation but retention of ataxic gait and the occasional use of a walking cane.

Currently, the patient is still being followed up with intravenous use of natalizumab (anti α-4-integrin monoclonal antibody),[16] and presents partial remission of symptoms in the inferior limbs and no further relapses to the date of this report.

DISCUSSION

The authors consider this case worthy of scientific highlight for two main reasons: first, because of the extensiveness of the physical exam involved, which exposed the involvement of two very different regions (and different sides) of the brainstem, causing distinct semiological findings. This is of note because the involvement of the trochlear nucleus is rare (most of the causes of IV nerve palsy are usually of lesions of the cranial nerve itself).[17,18] The second reason is to emphasise the so called clinico-radiological paradox, a fundamental challenge where new relapses in a MS patient with an organic substrate might comprise very small areas, to the point of not being recognised as new lesions in the MRI. Despite the use of gadolinium,[19] there is always a chance of disease activity in the normal appearing white matter.[20]

CONCLUSION

The authors reckon that in MS cases where semiology unquestionably denotes brainstem lesion, the decision for acute treatment should be based not only upon radiological confirmation, but mainly on the clinical manifestations. This is pivotal because truncal lesions have the potential to cause permanent and considerable sequelae and are independent indicators of worse prognosis if not promptly treated.[21]

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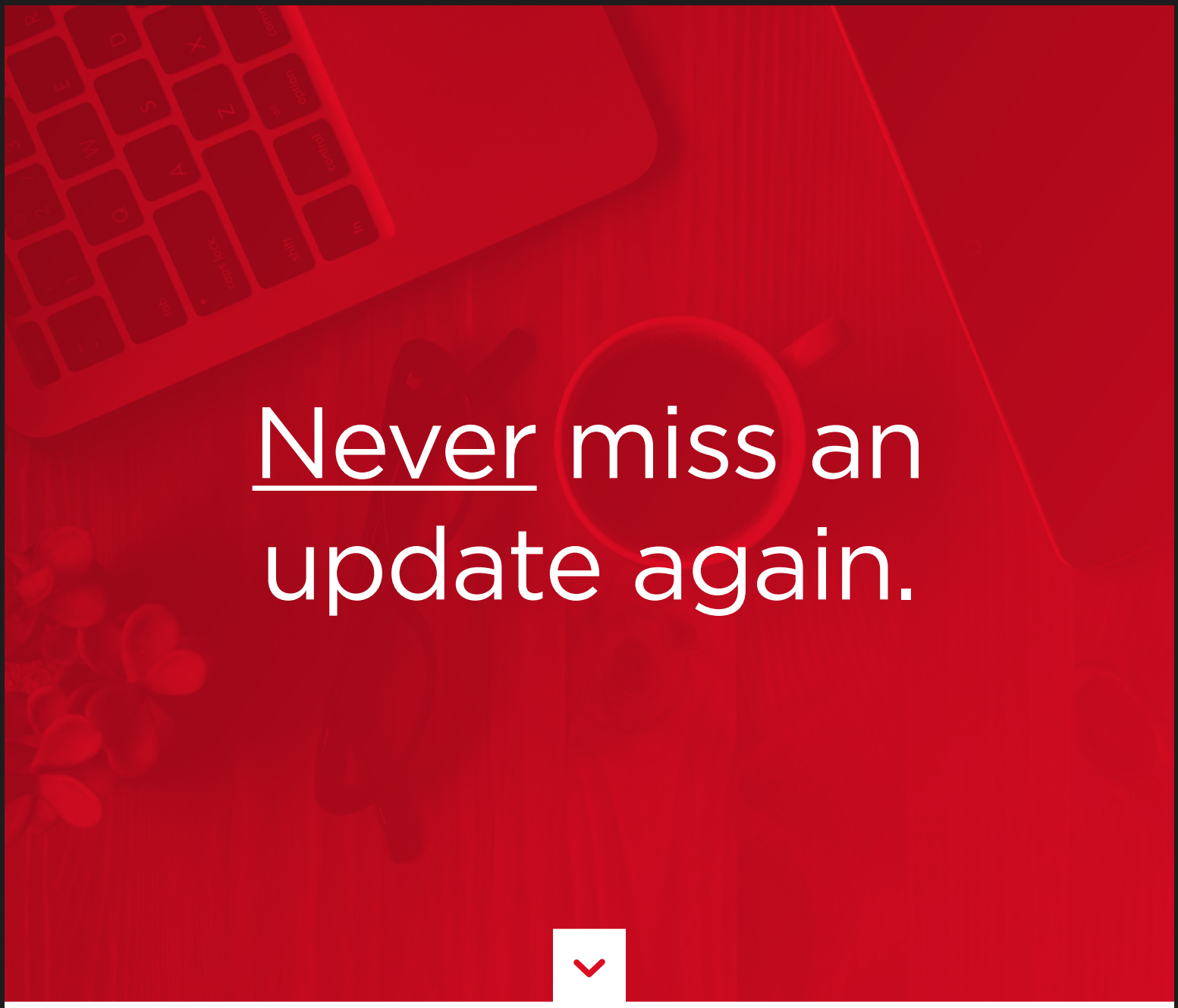

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