EMJ INNOVATIONS

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GIANT Health Event 2021

EDITOR'S PICK

Augmented Reality Can Improve Accuracy in Identifying Botulinum Toxin Injection Sites

INTERVIEWS

Martin Savage and Christina Furtado share their experiences and hopes in innovative aspects of healthcare

Contents

"From the use of closed-loop therapy to treat medication-resistant depression, to the application of clustered regularly interspaced palindromic repeat technology in patients with transthyretin amyloidosis demonstrating encouraging results, last year's discoveries are a testament to the resilience and innovation in the face of adversity."

Editorial Board

VIEW IN FULL ←

Aims and Scope

EMJ is an online only, peer-reviewed, open access general journal, targeted towards readers in the medical sciences. We aim to make all our articles accessible to readers from any medical discipline.

EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

EMJ is published quarterly and comprises review articles, case reports, practice guides, theoretical discussions, and original research.

EMJ also publishes 16 therapeutic area journals, which provide concise coverage of salient developments at the leading European congresses. These are published annually, approximately 6 weeks after the relevant congress. Further details can be found on our website: www.emjreviews.com

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- Guidance from an Editorial Board consisting of leading authorities from a wide variety of disciplines.
- Invited contributors are recognised authorities from their respective fields.
- Peer review, which is conducted by EMJ's Peer Review Panel as well as other experts appointed due to their knowledge of a specific topic.
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Front cover and contents photograph: London, United Kingdom, home of the GIANT Health 2021. © vichie81 / 123rf.com

EMJ Welcome Letter

Dear Readers,

In introducing the 2022 issue of *EMJ Innovations*, I would like to take the opportunity to wish you a very happy and healthy 2022, full of creativity, pioneering research, and great discoveries that help make the world a better place.

Looking back at 2021, COVID-19 was, once again, a focal point in research and healthcare, with leaps of progress made not only in vaccine development but also in new drugs against COVID-19. With the Omicron variant of SARS-CoV-2 sweeping through Europe and the world, the future still seems to be uncertain. This is not to say, however, that 2021 has not been an exceptional year for innovation in healthcare and great advances in every frontier of medicine. From the use of closed-loop therapy to treat medication-resistant depression, to the application of clustered regularly interspaced palindromic repeat technology in patients with transthyretin amyloidosis demonstrating encouraging results, last year's discoveries are a testament to the resilience and innovation in the face of adversity.

In December 2021, our Editorial team attended the GIANT Health Event in London, UK, which set the theme for the cover of this issue. Over 2 days, a number of innovators discussed technological advances in healthcare, from progress made in telemedicine to the latest wearable technologies. Our featured articles herein exhibit the importance of augmented reality and virtual simulations across different fields of medicine. We are proud to bring you a summary of the key highlights in this issue and we hope that you enjoy reading them.

As always, our in-house Editorial team, alongside our Editorial Board and peer reviewers have been major contributors in the quality of these articles and I would like to thank them for their immense contributions. We look forward to bringing you the latest developments in medical innovations throughout 2022 and welcome you to submit your own research to our journal.

Koutsouki

Evgenia Koutsouki, PhD

Editor

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Foreword

Dear Colleagues,

Welcome to the latest edition of *EMJ Innovations*. Several trends continue to be evident in healthcare currently, as we strive towards the goal of quantifiably improved health outcomes. One of these general trends is the increased incorporation of technology, some of which might come from unexpected areas. Another is the shift towards systems that can deliver personalised and precision medicine.

My Editor's Pick from this edition, titled 'Augmented Reality Can Improve Accuracy in Identifying Botulinum Toxin Injection Sites', incorporates both of these current trends. It looks at whether augmented reality (AR) can deliver superior accuracy with facial injection sites, when compared to the traditional approach reliant upon the memorisation of anatomy diagrams. The AR application used in this article was repurposed from a possibly unexpected source: the original design was a smartphone application for developing recreational social media filters. This enabled the creation of a face filter that overlaid facial muscles and injection sites using the subject's camera. Traditionally, injection sites are identified through learning the anatomy of the one-size-fits-most 'standard' face of medical diagrams. The authors look at how this use of AR could provide a system for a more personalised approach and consider the impact on outcomes from this.

Also touching on these trends is the article on 'Current Therapy in Inflammatory Bowel Disease: Why and How We Need to Change', which offers a comprehensive review and evidence-based discussion on treatments in the two major forms of inflammatory bowel disease: Crohn's disease and ulcerative colitis. After consideration of therapeutic limitations, it proposes how artificial intelligence-based multi-omics analyses may be used to implement precision medicine.

We look forward to seeing how these trends further develop in 2022, and hope that the content included in this edition of *EMJ Innovations* provokes not only thought, but also discussion and collaboration in a range of areas.

Best wishes,

Rachel Thomas

Doctor and Medical Author, Independent Health Consultant in Health Innovation, London, UK

A Review of the GIANT Health Event 2021

Evan Kimber
Editorial Assistant

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THE FOREFRONT of medical research has once again been dominated by advances in understanding the COVID-19 pandemic, but a deeper look reveals significant progress in multiple modes of futuristic clinical knowledge and practice. The stage was set in London, UK, at the GIANT Health Event 2021, harnessing a hybrid model of attendance giving delegates the opportunity to learn about progress in several hot topics in healthcare and technology.

Labelled Europe's largest and most valuable gathering in healthcare innovations, the 7th annual GIANT Health Event was opened by Shafi Ahmed, an award-winning cancer surgeon at the Royal London Hospital, UK, and current Chairman of GIANT Health. Fittingly for a modern technology gathering, this event provided contemporaneous virtual and in-person attendance options, labelled by Ahmed as "the model of the future." He elaborated: "It has to be hybrid; there has to be a way we bring people together with the option of flexibility," predicting that "this will happen in 2022 and beyond."

The main vision of the event is "to improve the health and well-being of people worldwide, by promoting healthcare innovation and supporting health-tech entrepreneurs," with informative sessions feeding into this. The audience enjoyed valuable updates on a range of topics, from progress in the digitalisation of integrated care systems and patient-centred healthcare, to precision medicine, and the current digital challenges facing healthcare. Overarching themes in the event included hopes for improved screening initiatives to allow early identification of malignancies, and better accessibility of healthcare via provision of remote technology.

The Main Stage, one of four live streaming sites of the congress, hosted a selection of enlightening presentations on the first day. Discussing the changing landscape and decentralisation of clinical trials, emerging solutions, and new ways to conduct these in-part or completely virtually, were discussed in more detail. Data on participant recruitment, travel, and drop out were used to argue in favour of remote trials taking place, ahead of being held at traditional test centres. This is a model gaining traction in the pharmaceutical world, likely due to the improved patient engagement and the insights digital tools can provide. The presenters explained that in 2018, around 10% of all the trials in Europe and North America exhibited an element of decentralised technology, and that this figure is expected to rise exponentially and reach one in three trials by 2025.

Turning towards the new frontiers in precision medicine, a session concentrating on brain-computer interfaces discussed the use of artificial intelligence for reading and writing neural signals in real-time. A large proportion of the session centred around neuromodulation, and its role in altering nerve activity by delivering electrical stimulation directly to a target area. This presentation clarified that future research, set to

"It has to be hybrid; there has to be a way we bring people together with the option of flexibility"

affect neurostimulation devices on the market and those yet to be released, will be guided by advances in the use of electrophysiology and action potentials to signal, rather than biochemistry.

Jumping across to the third stage, an informative talk on technology innovations to tackle hospital waiting lists was given by Mark Ratnarajah, a former practising paediatrician. Addressing the growing problem of waiting lists, which has been escalated by the COVID-19 pandemic, the presenter discussed the employment of risk stratification methods, such as outlining the successful use of artificial intelligence to identify and prioritise patients in the north of England.

Among topics discussed on Day 2 was wearable technology to support ageing. According to data presented by Katherine Church, Chief Digital Officer for Surrey Heartlands Integrated Care System, UK, 42 National Health Service (NHS) integrated care systems will be operating across the UK by April 2022, accommodating the caring requirement for large elderly populations. Louise Rogerson, a physiotherapist specialising in neurological conditions in older people, spoke about remote monitoring systems designed to help healthy ageing, and keep the elderly at home for longer. Underlining some of the barriers to healthy ageing. Rogerson stated: "People looking after older people who are declining, are declining themselves." She showed her support for novel therapies and technology to provide support in this discipline: "For me, technology needs to be more embedded in daily life," going on to stress the hard work that is necessary to allow healthy ageing. She urged listeners not to accept deterioration, and to adopt a shift in mindset from using technology to monitor failings in the elderly, and their progress. Concluding remarks centred on the hopes for emerging technology monitoring diagnostics in aspects like frailty and posture, and providing analytics to healthcare professionals to compliment early interventions, ahead of reactive responses to events like falls.

In his final remarks, bringing the congress to a close, Ahmed thanked the near 2,500 face-to-face attendees combined from both days, and the countless others accessing virtual content. Without a doubt, this pioneer platform of disseminating knowledge proved a success. It is expected that the forward-thinking content shared will continue to make waves in the ever-advancing pool of healthcare technology, sparking conversations and focusing approaches amongst the associated investors, researchers, and wider scientific communities. ■

Interviews

EMJ spotlights two clinical experts, Martin O. Savage and Christina Furtado. Though specialised in different fields, these individuals share a passion for realising the promising future of medical innovation.

Featuring: Martin O. Savage and Christina Furtado.

Martin O. Savage

Professor Emeritus in Paediatric Endocrinology, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry; Professor of Paediatric Endocrinology, London Clinic Centre for Endocrinology; Professor, Queen Mary University London, UK.

Q1

What led you to pursue a career in paediatric endocrinology, and at this stage in your career what continues to captivate your interest?

I was attracted to paediatric endocrinology as it concerns the whole body, rather than a single organ, and because of the logical nature of its concepts. I started to train in medicine late having secured a place at Magdalene College, Cambridge, UK, to read modern languages; I then changed to natural sciences before studying clinical medicine at St Bartholomew's Hospital, London, UK. Consequently, original scientific disciplines were a challenge. Endocrinology has a rational and logical progression with changes and mechanisms identifiable through varying biological pathways. This appealed to me.

I am still captivated by the disciplines of clinical assessment linked to genetic analysis for diagnostic accuracy. Clinical skills remain essential, although some geneticists down-play their importance and favour genotyping as the new diagnostic grail. Technology does not work without the human component needed to exploit its power and potential.

Q2

Are there any exciting developments on the horizon in the field of phenotype–genotype relationships that you are aware of and classify as particularly noteworthy?

Genetic investigation is still a developing field and in certain areas such as growth and puberty disorders, no clear phenotype–genotype relationships have yet been established.

However, in some areas such as congenital adrenal hyperplasia and multiple endocrine

"The most important word in academic activity is 'collaboration', allied to the human effort and determination for such collaboration to produce meaningful results. "

neoplasia, phenotype–genotype relationships are established and genotyping can lead to clear clinical decisions regarding therapy and management. The finding of a mutation of the *RET* proto-oncogene on chromosome 10 in a child with features of the multiple endocrine neoplasia Type 2B syndrome is a clear indication for prophylactic thyroidectomy before medullary carcinoma of the thyroid becomes established. In disorders of growth hormone (GH) action, mutations in genes encoding key functional proteins have clarified physiological mechanisms. This is a fascinating field of development.

Q3

Having lectured in more than 60 countries worldwide, where are the real hotspots in paediatric healthcare that influenced you the most? Which areas do you see leading the charge in provision of novel therapies, for example in the specialty of chronic inflammatory diseases?

I have been very fortunate to lecture in 60 different countries. The range of experience and expertise throughout the world is extremely wide. There is still an important basic need to understand fundamental clinical skills in many countries. But the eagerness to learn is striking. Western countries have the experience and resources to develop and use experimental therapies, and in an academic environment research projects are permitted to proceed and fail if necessary. This element of risk-taking is largely absent in many countries where research is either not practised or poorly developed.

Chronic inflammatory diseases such as malnutrition, sickle cell disease, and thalassaemia are by definition more prevalent in countries with reduced financial resources. The breakthroughs in their management will come through collaboration with wealthier scientific institutions. The most important word in academic activity is 'collaboration', allied to the human effort and determination for such collaboration to produce meaningful results.

Q4

Your experience researching growth disorders includes publication of the first human case of an *IGF-I* gene defect in 1996. As a pioneer, were there any challenges or barriers you recall overcoming to showcase this work, and what advice would you give today to a clinician working in uncharted territory or areas with significant gaps in literature?

The child with the *IGF-I* gene defect was referred to our group because of our declared interest in disorders of GH action. I was very fortunate to be able to collaborate with a high-quality molecular biologist, Adrian Clark. The child had a precise phenotype, i.e., low birth weight, short stature, microcephaly, deafness, and precise biochemical determinations suggested a defect of the *IGF-I* gene. Collaboration with Clark led to sequencing of the *IGF-I* gene that demonstrated deletions of exons 4 and 5. This was a classic example of the combination of clinical assessment, biochemical determination, and genetic sequencing leading to the discovery of a new human disorder.

My advice to a clinician working in uncharted territory would be to use meticulous clinical assessment techniques, and to find a talented molecular scientist who is equally interested in the clinical field, whether it be growth disorders or abnormal puberty. Collaborations are most successful and enjoyable when friendship and mutual trust develops between the two or three key investigators.

Q5

As an educator, where can we expect to see your focus lie in the coming years? Are there any particular areas that you would encourage younger clinicians to research?

Education remains an enormous challenge, largely because its effects are difficult to measure quantitatively. In terms of teaching, my commitment is essentially towards clinical skills and diagnostic guidelines in basic endocrine disorders such as growth and puberty in broad terms. I am inspired and fascinated by working in different cultures. Within the speciality of paediatric endocrinology, which fortunately is very broad, I would advise a young doctor to develop an interest in particular in growth

disorders, abnormalities of puberty, and adrenal disorders to name a few. A higher degree such as a laboratory-based PhD is a key step in acquisition of research skills for the future.

Q6 What do you consider your greatest achievement from your involvement as General Secretary of the European Society for Paediatric Endocrinology (ESPE)?

ESPE was founded in 1962, when the first Annual Meeting was held in Zurich, Switzerland, with 30 founding members attending, led by Andrea Prader of the Kinderspital. During its first years, it had the aura of a somewhat exclusive club with a constitution describing distinct administrative barriers to membership, and the precise geographical restriction of European countries or those bounded by the Mediterranean having access to membership. When I became secretary in 1997, paediatric endocrinology was a growing paediatric sub-specialty and the annual ESPE meetings had grown in size to several hundred delegates, yet membership was still relatively restricted. There was clearly a mismatch between the demand for membership and the availability of positions. The constitution needed changing and support from the voting membership was necessary to do this. Delegates from outside the geographical boundaries were aiding the financial viability of the society and also contributing scientifically to the annual meetings. A change in the constitution, removing geographical barriers and allowing easier applications for membership, resulted in the growth of ESPE and led to the open, successful, global society it is today.

Q7 How have you contributed most to the increased awareness of growth disorders, and particularly Cushing's syndrome?

Publications are essential for an academic unit to become successful. As an arts graduate manqué, I have been fortunate in being able to write, and to enjoy writing. Communication skills in lecturing together with the adoption of a specific area of interest such as GH resistance offered opportunities to establish the reputation of the unit as one committed to the diagnosis and treatment of growth disorders. The recruitment of highly skilled junior and senior staff helped enormously, as our publications and lectures were appreciated in the highest quality scientific meetings. The unit at St Bartholomew's Hospital, London, UK, was never large, but a relatively small number of committed clinicians and scientists worked for each other and when success came, such as with the *New England Journal of Medicine* (NEJM) publication of the *IGF-I* gene defect in 1996, enthusiasm was redoubled and helped build the momentum of a successful department.

Our interest in paediatric Cushing's syndrome stemmed from one fundamental advantage: that of working with a world-class department of Adult Endocrinology at St Bartholomew's Hospital led by Michael Besser. I was attracted to work there for this reason, and the advantages were enormous compared to working in an isolated children's hospital. The adult department had world-wide expertise in Cushing's syndrome and our interest in paediatric Cushing's resulted in referrals of children. Again, our reputation stems directly from amicable and productive collaboration between paediatric and adult specialists.

Q8 What are the most significant changes you have witnessed in the field of paediatric endocrinology over the course of your career?

The biggest change must be the emergence of molecular science as a diagnostic discipline that is now widely available to clinicians. This change occurred in the 1980s. One of the most dramatic examples is the disorder of classical GH resistance, known as Laron syndrome, after Zvi Laron, Tel Aviv, Israel, who first described it in 1966. The phenotype is striking, with extreme short stature with most parents being consanguineous. The first human GH assay was published in 1963 and Laron, who had experience with this disorder from 1958, demonstrated that three affected siblings had high serum GH values, rather than low values which the phenotype resembling hypopituitarism would suggest. Consequently, Laron syndrome became known to paediatric endocrinologists around the world as a probable genetic disorder, but of unknown aetiology. It was in 1989 that the first homozygous mutations of the GH receptor were identified. Candidate gene sequencing had demonstrated the causative defect and established the key role of the GH receptor in the regulation of human linear growth. ■

Christina Furtado

Mental Health and Wellness Specialist, guard.me International Insurance; Master of Arts in Counselling Psychology (MACP); practising member of the Canadian Psychological Association (CPA) and Ontario Association of Mental Health Professionals (OAMP).

Q1

What led you to pursue a career in mental health and wellbeing? What continues to inspire you today?

I started my career in education working primarily with individuals with learning disabilities, both diagnosed as well as some more self-endorsed issues. Working with these individuals by means of coaching and encouragement has always been part of the foundation of what I do.

When I continued pursuing more of a refined educational stream of my own personal and professional growth, I found myself diving into mental health. I had more of a motivation within anxiety-related disorders, because of who I was already working with and seeing. I found myself falling in love, to be honest, with understanding more about the struggles of individuals living with addictions. So many of these individuals also had anxiety, depression, or post-traumatic stress disorder, amongst so many other layers of complexity in what they were experiencing. I am really just grateful for the stories that I have heard, and the stories that were shared with me.

I wanted to pursue more in that line of work, taking it one step further and using the experience that I gained and the stories that I heard to better educate others on reducing the stigma and building awareness for these individuals that we see and have labelled so disgustingly, for a lack of a better word. These individuals have lived a life of trauma and pain that needs to be understood with compassion and not judgement. I've taken that mission, both personally and professionally, to whatever platform I am given the pleasure to be on.

Q2

A lot of your work is committed to providing mental health care in students; how has your approach shifted in recent years with the latest improvements in technology?

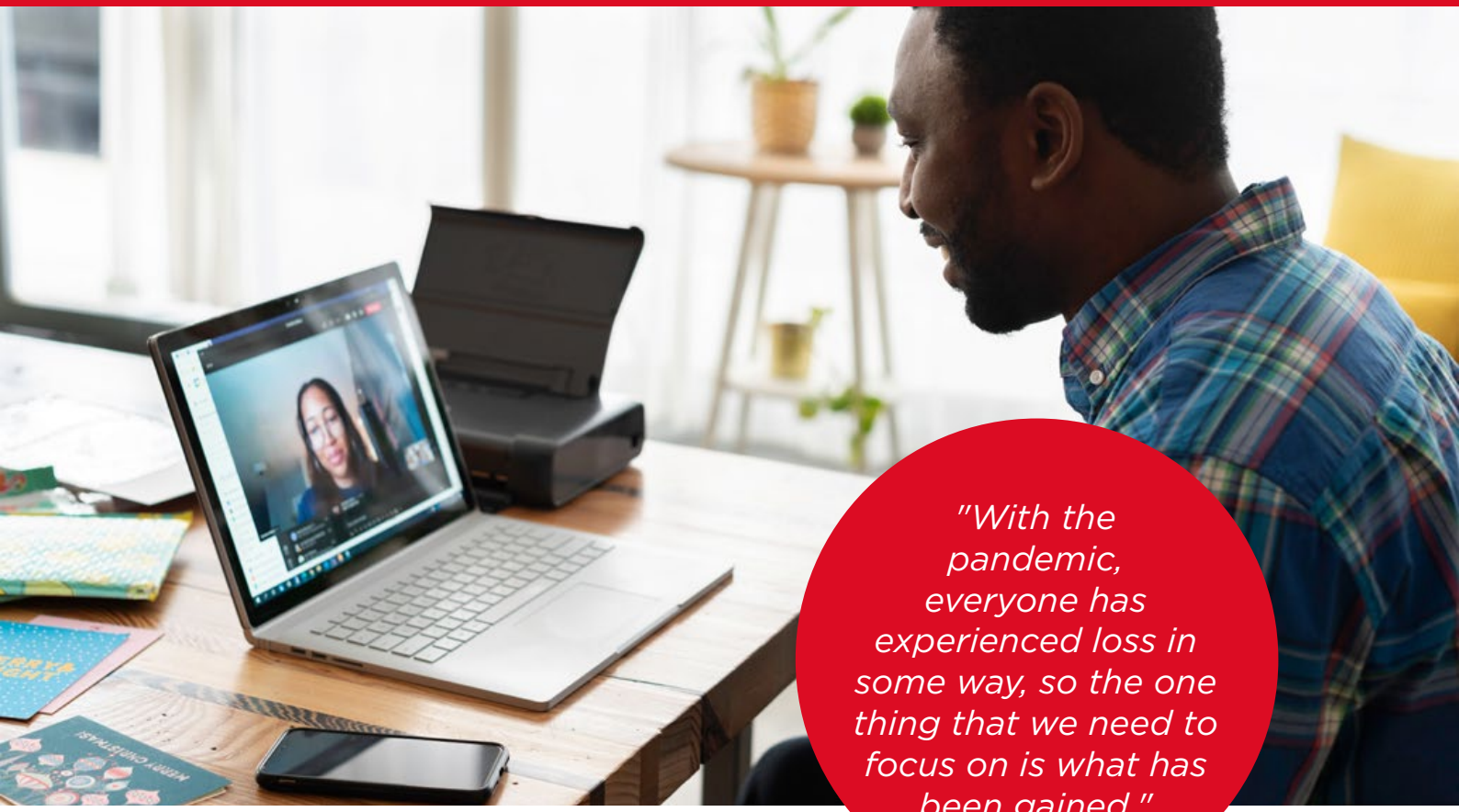
Well, one of the main premises of any counselling or mental health is about meeting someone where they're at; not being there to fix things, but to provide an individual with options. The avenue that I've seen really gain momentum and shift the paradigm in providing support and awareness is the increase in options and resources available to clients.

With the pandemic, everyone has experienced loss in some way, so the one thing that we need to focus on is what has been gained. This mind shift, looking at what has been gained, focuses on these options in terms of providing people with accessible resources, regardless of where they are at; providing means of counselling and raising awareness through use of digital access and virtual platforms has really allowed this shift to take place.

Q3

You were involved in a webinar based on 'the digitalisation of mental health'. What were the key messages delivered in this session?

When it comes to talking about such an intimate and private experience, which is what mental health is, it is unique to the individual, and often comes with that self-stigma: "Is someone going to understand me? Is someone going to judge me?" People start to build up walls, not wanting to share much, or not being comfortable reaching for support, regardless of this being educational or treatment based.



"With the pandemic, everyone has experienced loss in some way, so the one thing that we need to focus on is what has been gained."

When we look at a digital model, this could be counselling directly, it could be psycho-educational workshops, webinars, seminars; it's building a platform of education to raise awareness and create change. This adds a level of comfort for the individual on the opposite side of the screen, the individual that is reaching out, in whatever way, for whatever reason and purpose. It can add that level of autonomy where you don't have to share who you are.

There's no judgement of what someone else is going through; even facial expressions can indicate how individuals are receiving information. In this respect, digitalisation can really add a level of comfort for an individual by matching exactly the willingness, readiness, and awareness they are experiencing at the time. When you have this access, through various resources at any particular time of day or night, it really aligns with where the individual is at, and what they need. Mental health is not a nine-to-five. It's not a Monday to Friday. It comes in waves, tsunamis for some. So, having access to this digital aspect can greatly improve the experience that individuals have; it's where they need it the most, when they need it the most, in a way that they need it that is meaningful and can actually create change for them.

Q4

Serving as a member of the Canadian Psychology Association (CPA) and Ontario Association of Mental Health Professionals (OAMP), how are these organisations keeping their health initiatives up-to-date with telemedicine and provision of care on the back of the COVID-19 pandemic?

Both associations share the same idea, the same intention. This is to have a means where industry leaders and colleagues within the field across Canada (the OAMP is strictly provincial) can collaborate. They help to really ensure a standard of practice; while we have our code of ethics within the profession, this allows us a means to collaborate and professionally develop. When it came to COVID-19 and the transfer in treatment towards a more virtual model (which, let's be honest, existed but was never the primary means in how we provided care), there was still a debate as to this model's efficiency and its effectiveness in the industry.

These associations allowed for this debate to happen in a respectful way, but also provided education in the midst of the pandemic. They aided the transfer of care, which needed to happen, as we all became more comfortable

with this modality. They provided webinars and other research, as well as guidance for those that were a little bit more hesitant. This has helped clinicians get more comfortable and really gain an appreciation for their adapted duty of care. Our duty of care is to not to tell a client: "This is the best way for you", but rather to hear the client and say: "I'm here for you in what you feel like is the best form of care, and is suitable to your needs."

Knowing that our whole reason for going into the profession is to be that teammate of support, or that resource of care, a lot of individuals have been forced to shift gears into a more virtual way of delivering service. These associations provided us with information, which supported us in ensuring that these methods were still effective for clients. They provided webinars and other professional development training opportunities for those that weren't as comfortable with the transition as others, because that's what we've always done. Aligned with that, they have really taken a front seat drive to help educate the educators.

Yes, we don't necessarily have that face-to-face, non-verbal dynamic that we have relied on to get a sense of where a client is with their comfort level, or even transparency with what they're sharing (or not sharing) as cues to help guide us within the sessions. We haven't lost it; it has just morphed into something different. Frankly, I have appreciated the ability to be creative in how I work with my clients, especially in a virtual model; it really allows for a different type of rapport, and challenges the comfort zone that we all get stuck in within our careers. The counselling career is no different, a mental health career is no different.

Q5 Are there any particularly innovative approaches or techniques you are excited to transition into standardised practice in the near future?

I think the one thing that we have seen gain a lot of traction is how closely related our cognitive abilities are to actually resulting in change, and promoting change not only in ourselves but in others. So, cognitive processing therapy, cognitive behavioural therapy, dialectical behavioural therapy have all gained more traction since COVID-19, especially during this virtual model because so much of it can be done independently and then reviewed with guidance from a professional to really explore the various layers that are revealed through this independent work. That's one thing that we need to start seeing, and I'm excited to see a lot more of.

When it comes to anything mental health related, promoting change starts with the individual; there has to be a willingness from that individual, there has to be a readiness. For me, self-empowerment has really taken off, and that to me is exciting. That to me is a mindset that we have needed to see a shift to becoming more widespread than it has been in the past. To start seeing that now, as a focal point within the mental health field, empowering the individual, it needs to start that way. If you can help empower an individual on their journey, that to me is a recipe for success.

I think the gift of COVID-19, and I know it sounds like an oxymoron, has presented the opportunity to change an individual's mindset. When you come from a mindset of loss or failure, you create barriers towards moving forward and personal growth. Growth only happens when you are uncomfortable and when there is uncertainty, and COVID-19 has really thrown a wrench in normalcy for so many people, allowing for progression. I see this as a positive in this sense.

Q6 From your experience working in addiction rehabilitation, do you think the 'online revolution' we are experiencing will have long-term implications? If so, how will these affect medical experts and their clients?

I think, from a professional standpoint, there can be positive gain with regard to a virtual model of treatment; I think that a sense of community and connection is critical to the recovery pathway of an individual living with an addiction. Addiction is a very isolating disease itself inherently, and this is where there is a concern for me. As much as there can be gained, looking at where an individual is at and how their particular experience of addiction might be keeping them isolated is important, as this is going to have an adverse effect. If individuals such as this continue to receive treatment virtually, this added isolation could have negative effects.

We focus on the successes of an individual in recovery, with them regaining a connection with self and others in a healthier way. Those that work in the field of addiction tell their clients that it is important, when looking at a recovery action plan, to change people, places, and things. This is something that can be applied to those wanting to make positive, meaningful, and sustainable life changes. If you don't have the opportunity to challenge the new habits, or the new ways of thinking, you don't necessarily know what triggers you have and how to ride the wave of that 'urge' and give-in to some of those triggers. This is particularly challenging when you're living more of a virtual life.

I think if there is that awareness of the possibility, then we can become more proactive and not reactive to things. We tend to be on autopilot, as humans we become more reactive versus proactive. I do feel that people within the industry, especially in treatment centres, are taking a more proactive approach by really building a foundation of success for the clients before they come into treatment, and maintaining that same care afterwards during the difficult journey to recovery.

We are prone to falling into similar habits, old, learned behaviours, and isolation is one of them. To continue to find encouraging means to offer that sense of connection and community, virtual platforms are what will allow for individuals living in recovery to continue to live in recovery, successfully.

Q7

What are your opinions on video consultation? Is it a sustainable method of meeting with individuals? Are there any dangers, problems, or benefits you have come across implementing these appointments?

I think that there are benefits with it being more accessible when a client is ready. With regards to intervening or any type of assessment, there is a lot to navigate in terms of time; this might include travel, schedules, things of that nature. Through virtual models the aspect of time is more valuable and immediate in the sense of people saying: "Yes, I've got 20 minutes right now. Let's get on a call!"

The difficulty lies with maintaining this as a primary means moving forward, and that not everyone has access. Many individuals might be unable to access a virtual platform, and this is going to be an issue. This is where, again, we need to look in a proactive way at what has been effective, which areas, and who are affected in a negative way, in order to access these particular resources and assessments.

Consultations are one of those resources, and we can't always assume that when an individual has an assessment or consultation, they are going to move forward with support. This is setting up an expectation that is going to be disappointing; not only for family members potentially, but also in the profession you can't have that expectation. Access, I think regardless of virtual or non-virtual environment, is the problem we face.

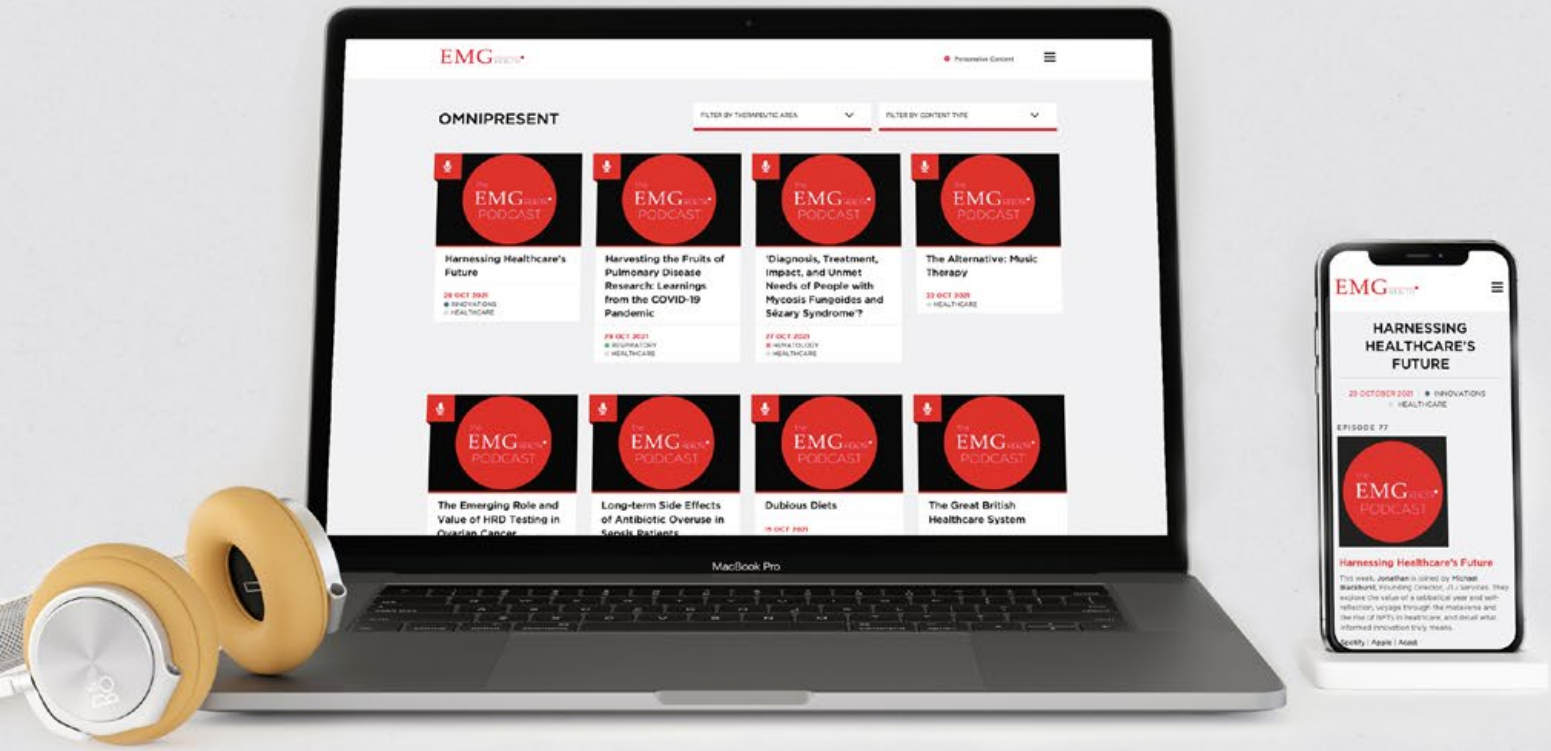
Q8

What advice would you give a younger-self or recently established clinician building a career in an increasingly digitalised field?

You can't save everyone. If you go into this profession with the idea and the hope that you are going to change millions of lives, you're not. It's important to have an appreciation and hope to create change, but not an expectation of creating change. It is about planting a seed for someone else to grow.

In clinical training we are always encouraged and really drilled with boundaries; while I had boundaries for my interactions with clients, I didn't have boundaries for my own expectations of what was going to come out of a particular therapeutic relationship. Looking back, training gave me a more grounded platform to be a better version of myself, not only within my counselling sessions and in counselling roles, but also outside of that.

This attitude allows clinicians to leave their problems at the door and not make somebody else's issues their own. As a human being, you have your own life, even being in this profession. You don't have the answers to everything. This experience allowed me to gain clarity as to what I was okay to carry through my day and what that I wasn't okay with. ■



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EMG HEALTH

A brain–computer interface (BCI) measures, analyses, and translates the activity of the central nervous system (CNS) into artificial output to to replace, restore, enhance, supplement, or improve natural CNS output

DEFINITION

BRAIN–COMPUTER INTERFACES

CURRENT BCI TECHNOLOGY

Invasive: detect electrical signals with electrodes on the surface of the brain cortex

Non-invasive: detect electrical signals on the surface of the scalp and metabolic activity from functional-MRI

FUTURE DIRECTIONS

Neural bypasses and bridges promising in rerouting signals around injured segments of the CNS

Adding sensory feedback to a BCI system will improve functionality

Personalisation for paediatric, adult, elderly populations (head shape and size)

'Artistic BCI' controlling an augmented or virtual environment

Brain fingerprinting for lie detection, estimating reaction time, controlling drones, instructing humanoid robots, and virtual reality

Integration of artificial intelligence and human interaction; syncing human decision-making with complex computer algorithms

Increase access through dry electrodes on wearables and minimally invasive biosignal acquisition devices

POTENTIAL APPLICATIONS

Treatment pathways:

CNS substitutes: target lost function from paralysis, stroke, or trauma. Harness myoelectric signals to use with robotic prosthetics or communication devices

Diagnosis: screen populations by ECG, identify individuals with degenerative diseases, detect tumours, diagnose mental disorders

Rehabilitation: post-stroke motor rehabilitation and deep-brain stimulation for Parkinson's disease, tinnitus, hallucinations, and migraine

Improve motor and cognitive ability

Patients with paralysis

Ageing populations

Allow **remote control of home appliances**

Improve **communication**

High-bandwidth neural interfaces could allow modulation of neural activity to provide proprioception to neuroprosthetic movement control

Control an **exoskeleton** to aid joints

BARRIERS:

- Surgical risks with invasive device implantation
- Battery life
- Transitioning from wired to wireless devices
- Immune response and risk of infection

All references can be found here.

Scientific Highlights in Innovation

The following scientific highlights have been selected to showcase key findings across a selection of therapeutic areas.

Long-term Consequences of COVID-19: 6 Months On

COVID-19 took the world by surprise in late 2019, pushing scientists to study the virus extensively and create an effective vaccine. Despite the numerous hours, weeks, and months of research there remains a lot that is not well understood about the deadly virus. The long-term health consequences of COVID-19 remain a mystery to doctors and not all risks are clear. Scientists in Wuhan, China, aimed to determine what some of the long-term consequences of COVID-19 were by conducting a large cohort study and assessing disease severity.

The study took place from January 2020 to May 2020 and involved a cohort of patients with COVID-19 discharged from Jin Yin-tan Hospital, Wuhan, China. Patients who had died before the follow-up, had been re-admitted, or had been discharged due to other conditions were not included in this study. In total, 1,733 patients were enrolled in the cohort study; 52% of this sample were men and the median age of patients was 57 years. Each participant underwent a series of questionnaires to assess their symptoms and quality of life.

Further to this, all patients had a physical examination, took part in a 6-minute walking test, and received blood tests. Methods used included a stratified sampling procedure to categorise patients as 3, 4, and 5–6 according to their highest seven-category scale during their stay at the hospital. Statistical models, namely a logistic regression model and a multivariable-adjusted linear model, were conducted to assess the link between disease severity and long-term consequences.

Findings revealed that fatigue and muscle weakness were the most common symptoms, found in 63% and 26% of patients, respectively. Additional findings uncovered that the mental health of 23% of participants was also affected, particularly resulting in anxiety and depression. The walking test demonstrated that 29% of patients had a walking distance less than the lower limit of the normal range and high severity scale result (5–6); 56% of these patients also had impairment of pulmonary diffusion.

The authors concluded that the most debilitating symptoms in patients with COVID-19 6 months after acute infection were fatigue, muscle weakness, sleep difficulties, anxiety, and depression. The more ill the patient was during their hospital stay correlated with the patient having more severely impaired pulmonary diffusion and atypical chest imaging manifestations. Overall, this study highlighted the importance of following up with severely ill patients with COVID-19 and providing long-term care after the initial COVID-19 infection. ■

Reference

Huang C et al. 6 Month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021;397(10270):220-232.

Randomised Trial Supports Hypothermic Oxygenated Machine Perfusion in Liver Transplantation

ACCORDING to recent findings, there is increased risk of complications of a biliary nature in liver transplantation when using livers obtained after circulatory death. A new study in a field with limited comprehensive research has revealed that hypothermic oxygenated machine perfusion leads to a lower risk of non-anastomotic biliary strictures, superior to conventional static cold storage. The use of the *ex situ* machine perfusion method shows real promise and would be integral to improving outcomes after organ transplantation. The ongoing study by van Rijn et al. has already been highly cited, reflecting the interest shown by many clinicians and their patients in this encouraging evidence.

In this multicentre, controlled trial, transplant patients were randomly assigned to receive their liver after either oxygenated machine perfusion or conventional static cold storage. The primary endpoint for both the machine-perfusion group and the control was the incidence of non-anastomotic biliary strictures within 6 months. There were 160 participants enrolled in the trial, with 78 receiving machine-perfused livers and 78 receiving livers from static cold storage (four did not receive a liver). Non-anastomotic biliary strictures occurred in 6% of patients in the machine-perfusion group and 18% of the control group, whilst 12% of the machine-perfusion group experienced post-reperfusion syndrome compared with 27% in the control group. Moreover, early allograft dysfunction was seen in 26% of the machine-perfused livers versus 40% for the static cold storage livers. Incidence of adverse events was similar across both branches.

When compared to conventional methods of preservation, those randomly assigned to receive machine-perfused liver grafts had a risk lower by two-thirds of developing symptomatic non-anastomotic biliary strictures within 6 months of transplantation. This protective trend was also exhibited in the lower risk of post-reperfusion syndrome and early allograft dysfunction. Moving forwards, the prevention of post-transplantation cholangiopathy in this way may not only increase the acceptance rates of liver grafts, but also improve the cost effectiveness of machine perfusion. The authors recognised that larger trials are warranted to detect an effect on survival rates after liver transplantation and risk of graft loss. ■

Reference

van Rijn R et al. Hypothermic machine perfusion in liver transplantation. N Engl J Med. 2021;384(15):1391-1401.

"hypothermic oxygenated machine perfusion leads to a lower risk of non-anastomotic biliary strictures, superior to conventional static cold storage"

Artificial Intelligence-Based Differential Diagnosis for Cancers of Unknown Primary

MODERN cancer therapeutics such as chemotherapy and immune checkpoint inhibitors are now highly targeted and often specific to the primary tumour in each case. Cancer of unknown primary (CUP) refers to a group of cancer diagnoses where the primary anatomical site of tumour origin cannot be determined, thus creating significant challenges with targeted therapies. In many cases, the primary is never determined even after extensive diagnostic work-up, which is both time- and resource-consuming and significantly delays the administration of appropriate treatment.

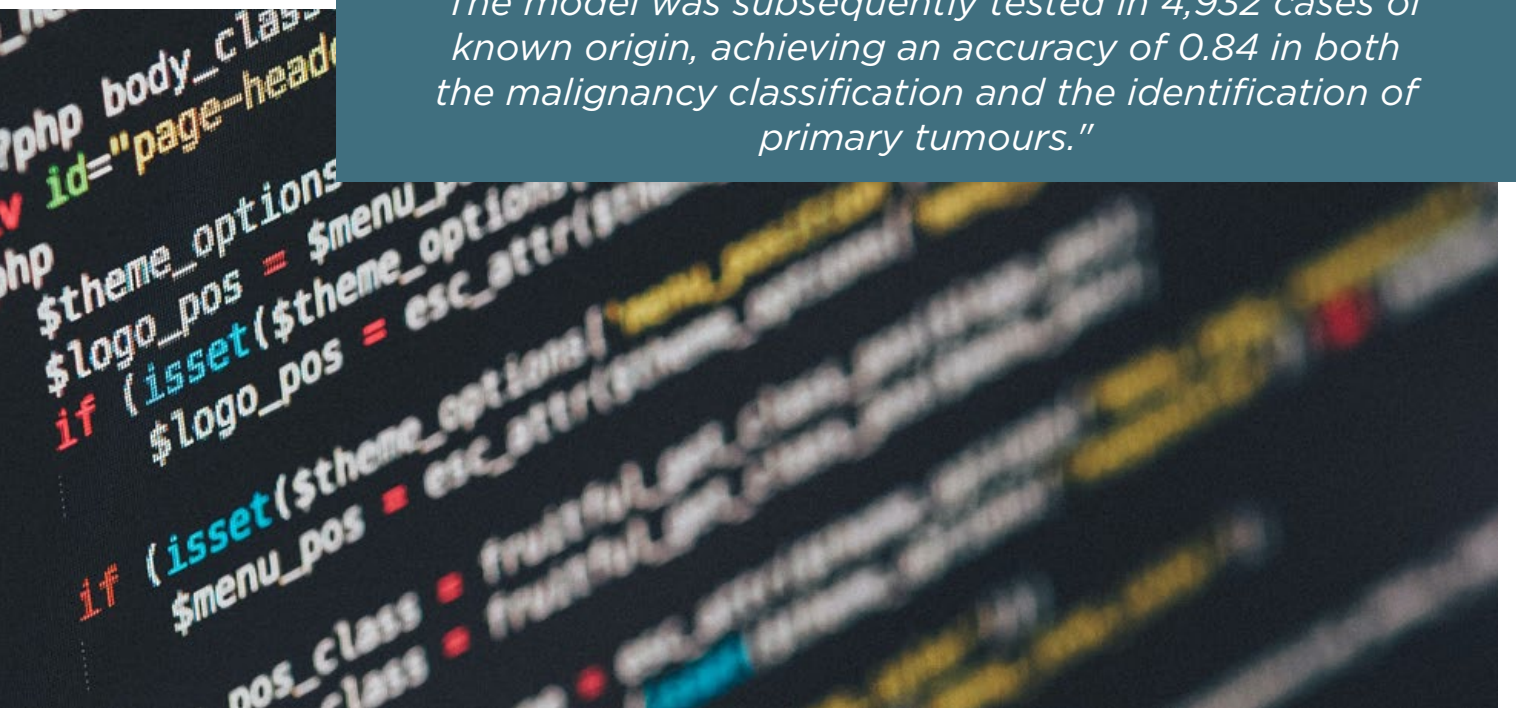
Researchers from Harvard Medical School, Boston, Massachusetts, USA, investigated the use of a deep-learning-based computational pathology algorithm called the Tumour Origin Assessment via Deep Learning (TOAD), which can be used to analyse histology slides and provide differential diagnosis for CUP. The multi-task deep model was educated using slide images of known primary tumours, spanning 18 common tumour origins. The model was subsequently tested in 4,932 cases of known origin, achieving an accuracy of 0.84 in both the malignancy classification and the identification of primary tumours. In external tests with images from other hospitals, the model achieved an accuracy of 0.79. The external tests allowed the researchers to test the adaptability of the model across different healthcare systems who use different histological sample preparation standards. Previous studies have demonstrated that pathologists often struggle to identify the origins of metastatic tumours when minimal clinical information is available. This model demonstrated the ability to make fairly accurate primary differentials even for challenging metastatic cases using only histology with patient gender data.

The proposed model represents a novel assistive tool to be used in complicated CUP cases. With future research, this could be used in conjunction with or instead of immunohistochemical analysis and extensive diagnostic work-up to reduce the occurrence of CUP. ■

Reference

Lu MY et al. AI-based pathology predicts origins of cancer of unknown primary. Nature. 2021;594(7861):106-10.

"The model was subsequently tested in 4,932 cases of known origin, achieving an accuracy of 0.84 in both the malignancy classification and the identification of primary tumours."



EVOQUE Tricuspid Valve Replacement System for Severe Tricuspid Regurgitation

"although all patients were at high surgical risk and initially had an NYHA Class of III or IV, technical success was at 92% with 0 deaths occurring during surgery"

TRICUSPID regurgitation (TR) is a condition where the valve between the right atrium and right ventricle does not close properly, causing blood to flow back into the atrium. Approximately 85% of adults may experience mild TR; however, issues arise when the condition is severe, causing distressing symptoms such as swelling of the abdomen, shortness of breath, and fatigue. One viable treatment option is transcatheter leaflet repair, although this might not be suitable for all; transcatheter tricuspid valve replacement (TTVR) may be a more appropriate option for a larger number of patients. This novel study, detailing a first-in-human experience of TTVR, aimed to investigate the safety and practicality of EVOQUE TTVR for treating patients with severe TR.

The lead authors of this study, Niel Fam, St. Michael's Hospital, University of Toronto, Ontario, Canada, and Ralph Bardeleben, Universitätsmedizin Mainz, Johannes Gutenberg Universität, Germany, shared their findings of this first-in-human experience testing EVOQUE TTVR. Scientists recruited 25 patients with severe TR, who were predominantly female with a mean age of 76 years, to undergo EVOQUE TTVR. The primary outcome was the technical success of the procedure, with consideration to the New York Health Association (NYHA) classification, TR grade, and severe adverse events at 30-day follow-up.

Results showed that, although all patients were at high surgical risk and initially had an NYHA Class of III or IV, technical success was at 92% with 0 deaths occurring during surgery. Additional findings demonstrated that at the 30-day follow-up there was 0% mortality, NYHA functional class was lower at I or II in 76% of patients, and 96% of patients had a TR grade ≤2+. Adverse events included major bleeding in three patients, two patients needing dialysis treatment, and one patient requiring pacemaker implantation.

Overall, this study demonstrated the effectiveness of EVOQUE TTVR in this first-in-human procedure. The results showed that EVOQUE TTVR has high technical success, significant clinical improvement, and few severe adverse events. Fam and Bardeleben acknowledged their small sample size as a limitation and suggested that larger studies are needed to confirm safety and long-term clinical outcomes. ■

Reference

Fam NP et al. Transfemoral Transcatheter Tricuspid Valve Replacement with the EVOQUE System: A Multicenter, Observational, First-in-Human Experience. JACC Cardiovasc Interv. 2021;14(5):501-11.

Adverse Obstetric and Perinatal Outcomes Compared in Programmed and Natural Cycle Frozen Embryo Transfer

OBSERVATION of singleton deliveries in Denmark has revealed how the outcomes of pregnancies differ with contrasting frozen embryo transfer (FET) protocols.

Asserhøj et al. performed a register-based study including all singleton deliveries after assisted reproductive technology in Denmark between 2006 and 2014. Outcome measures were assessed in the 1,136 deliveries, grouped by FET protocol into programmed FET (n=357), modified natural cycle FET (n=611), and true natural cycle FET (n=168). The obstetric outcomes assessed were hypertensive disorders in pregnancy, pre-term pre-labour rupture of membranes, placenta praevia, placental abruption, induction of labour, postpartum haemorrhage, and caesarean section. Meanwhile, the perinatal outcomes assessed were post-term birth, pre-term birth, birth weight, small for gestational age, and large for gestational age.

The study findings identified a significantly higher risk of hypertensive disorders in pregnancy, postpartum haemorrhage, and caesarean section after programmed FET compared with natural cycle FET (both modified and true natural cycle). A higher risk of experiencing birthweight >4,500 g was also observed in programmed FET versus natural cycle FET. Based on this study, the authors were able to conclude that programmed FET adversely affected both obstetric and perinatal outcomes. On the back of this discovery, the investigators recommended, where possible, endometrial preparation with the creation of a corpus luteum.

Moving forwards, randomised control trials of FET that compare programmed and natural cycles are warranted to clarify and further this research. Broadening the catchment area and participant recruitment requirements to include a more varied population will also benefit applicability of these findings. ■

Reference

Asserhøj L et al. Adverse obstetric and perinatal outcomes in 1,136 singleton pregnancies conceived after programmed frozen embryo transfer (FET) compared with natural cycle FET. Fertility and Sterility. 2021;115(4):947-956.

"The study findings identified a significantly higher risk of hypertensive disorders in pregnancy, postpartum haemorrhage, and caesarean section after programmed FET compared with natural cycle FET "

Augmented Reality Can Improve Accuracy in Identifying Botulinum Toxin Injection Sites

EDITOR'S PICK

Facial injection is a highly pressurised and challenging procedure for developing clinicians, with trainees traditionally studying medical anatomy diagrams and models. This paper by van Rhee et al., selected as the Editor's Pick for this issue, provides a forward-thinking look at the opportunities for augmented reality and personalisation in this field. The study investigates use of a smartphone app, which delivers overlaying filters, individualised to the face of the user, on muscles and botulinum toxin injection sites. The paper is a valuable contribution to those included in this journal, and is expected to provoke conversations amongst the EMJ readership.

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Abstract

Facial botulinum toxin injection is a skill developed with experience. Inaccurate injections of the toxin can cause local complications as well as patient distress. Trainees typically learn to perform facial injections following detailed study of medical anatomy diagrams. However, anatomy diagram depictions of a 'standard' face may not be generalisable to the varied facial anatomy of real patients. Augmented reality (AR) technology may provide a more individualised approach. In this study, an AR smartphone app, designed for the development of recreational social media filters, was repurposed to create a face filter that overlaid facial muscles and corresponding botulinum toxin injection sites onto the face of any subject detected by the supporting device's camera. The primary outcome was to determine if accuracy in injection site identification was superior using the AR app versus a standard facial anatomy diagram. Ten participants who were naïve to administering facial injections used both the AR app and anatomy diagrams to mark 10 injection sites on the face of a test subject using a makeup pen. The distance between these sites and the 'gold standard' injection sites as determined by an expert botulinum toxin practitioner was calculated. Participants were more accurate with the AR app than with the diagram, with average distance from expert-identified location 4.60 mm versus 6.75 mm, respectively ($p<0.01$). Further research is needed in optimising this technology prior to trialling its use in patients; however, AR has tremendous potential to become a useful adjunct for procedures requiring anatomical knowledge of facial muscles.

INTRODUCTION

Botulinum toxin is a neurotoxin produced by the Gram-positive anaerobic bacterium *Clostridium botulinum.* It acts by cleaving soluble N-ethylmaleimide-sensitive factor attachment protein receptor complex proteins in the presynaptic motor neuron, inhibiting the release of acetylcholine at the neuromuscular junction, and resulting in local chemical denervation.[1,2] Botulinum toxin injection is used to treat many neuromuscular conditions affecting the face, including strabismus, blepharospasm, hemifacial spasm, and oromandibular dystonia.[3,4] It is also used for cosmetic purposes in the elimination of vertical glabellar eyebrow furrows, horizontal forehead lines, and lateral canthal wrinkles.[5] Identifying the appropriate site for facial botulinum toxin injection is a skill developed with practise, detailed study of anatomy diagrams, and experience. Inaccurate injections of the toxin can cause complications, including blepharoptosis, brow ptosis, and facial asymmetry.[5] While these adverse effects are largely transient, they may be caused by an injection site inaccuracy of only a few millimetres[6] and result in distress for patients. This highlights the need for increased precision and replicability during injection. Beginners typically learn to identify injection sites through the study of medical diagrams of facial anatomy. These depictions of a 'standardised' face are not necessarily generalisable to the varied shapes and contours of the faces of patients.

A more individualised approach is needed, and emerging augmented reality (AR) software may provide a solution. AR is a variation of virtual reality, where a user's surroundings are supplemented, or augmented, by additional digital information. One of the most widespread applications of AR technology in today's society is the omnipresent 'face filter'. More than 4 billion people are active on social media platforms that support facial recognition software and face filters for recreational purposes.[7] This widely used technology has the potential to also lend itself to personalised medicine and act as an adjunct in facial botulinum toxin therapy.

Face filters make use of face meshes, or virtual representations of the face. When a subject's face is detected by a smartphone camera, features called nodal points such as the eye position, eye separation distance, nose position, and mouth position are extracted. These nodal points are then linked through vertices to create a virtual face mesh, applicable to any face recognised by the camera. When a face tracker and the face mesh are combined, they produce a surface that can detect facial movements. A face filter overlays an effect or image onto the face mesh, producing a form of AR where the virtual image is superimposed onto the subject's own face in real time.[8]

AR apps using facial recognition and face filters could enable mapping of the optimal location for injection onto any face recognisable by the supporting device's camera. This technology could improve the speed and accuracy when identifying sites for facial botulinum toxin injection, while accounting for anatomical variation across subjects. This may not only function as a useful learning tool for trainees in facial injection but reduce complication rates of the procedure in clinical practice. A recent study demonstrated that a dedicated AR guide for botulinum toxin injection, developed using prior radiological imaging of patients, was sufficiently accurate for use in clinical practice. Accuracy was up to 3 mm for all facial regions, suggesting that use of AR technology is becoming more relevant and feasible in this domain.[9]

In this study, an AR smartphone app designed for the development of social media face filters was used to create a filter that overlayed facial muscles onto the face of a subject detected by a smartphone camera. Accuracy in identifying facial injection sites using this AR smartphone app was compared to that using a standard medical anatomy diagram in participants naïve to administering facial injections. The aim was to establish if injection site identification accuracy was superior using the AR smartphone app versus a standard facial anatomy diagram. Secondary outcomes were time taken to identify injection sites, confidence using either tool, perceived usefulness of the tools, and perceived accuracy with the tools.

METHODS

A consultant neurologist and qualified botulinum toxin practitioner with extensive experience

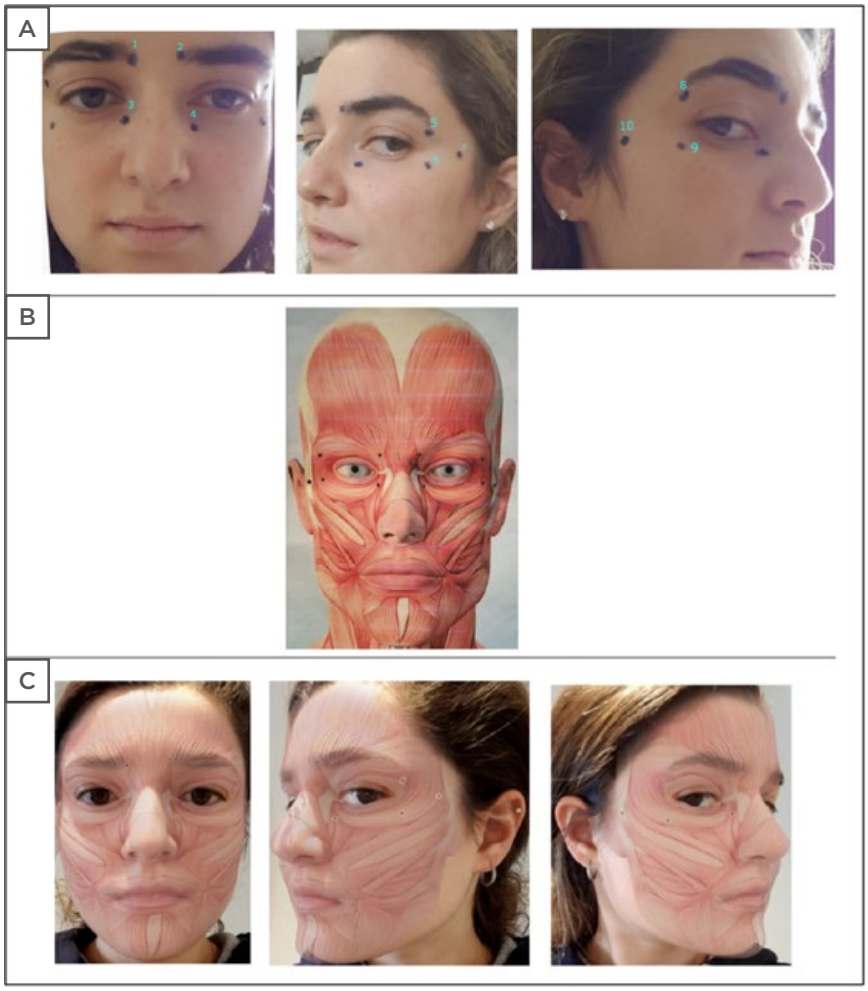

Figure 1: Injection site locations on the test subject, anatomy diagram, and the augmented reality image.

A) Sites for injection on the face of test subject as marked by the expert botulinum toxin practitioner. **B)** Anatomy diagram provided to participants with injection sites marked by expert botulinum toxin practitioner. **C)** Sites for injection on the face of test subject as viewed using the augmented reality app.

in administering botulinum toxin injection for facial dystonia identified and marked 10 points appropriate for botulinum toxin injection on the face of a test subject (Figure 1A). The equivalent 10 points were also marked on a facial anatomy diagram (Figure 1B). These were taken to be the 'correct' sites for botulinum toxin injection as per the expert opinion.

The AR face filter was created using Spark AR studio (Facebook, Menlo Park, California, USA).[10] The basis for the filter was the same anatomy diagram on which the 10 injection sites were demarcated by the expert. When accessed through the Spark AR Player smartphone app, this face filter allowed the facial muscles displayed in the anatomy diagram and the expert's 10 injection sites to be mapped onto any face recognised by the app in real time (Figure 1C).

Ten participants who were naïve to administering facial injections used both the AR app and a medical anatomy diagram to mark the 10 injection sites on the face of a test subject using a makeup pen. No real botulinum toxin injection was administered. The AR app was tested either on an Android smartphone (Google, Mountain View, California, USA) or an Apple iPad (Apple, Cupertino, California, USA). Half of the participants performed the task with the diagram first and the other half with the app first in a counterbalanced fashion. Accuracy of markings and time taken to complete the task were measured. The same test subject was used for all participants.

Participants completed a short survey to compare confidence using either tool and perceived usefulness and accuracy of both tools following the task. They were asked to rate their confidence using the AR app and the anatomy diagram on a scale of 0–10, rate the perceived usefulness of both tools individually and combined on a scale of 0–10, and their perceived accuracy with both tools on a scale of 0–10. They were asked which tool they preferred and whether they would consider using the app for real administration of botulinum toxin injections. Participants were invited to leave comments on their experience of using the app. The subjective opinion of users was obtained to assess the likelihood of users adopting this technology for its intended purpose.

To calculate accuracy, photographs were taken of participants' markings on the face of the test subject. These images were compared with the images of the expert botulinum toxin practitioner's markings using graphics software Inkscape (Software Freedom Conservancy Inc., New York, USA). Accuracy values for all 10 sites were obtained by measuring the distance between participant injection site mark and botulinum toxin practitioner's injection site mark to the nearest 0.5 mm. Injection sites 1–4 were classed as having medial locations, and sites 5–10 were classed as lateral locations (Figure 1A). The corresponding muscle groups for each injection site are denoted in Table 1. Participants had a mean age of 24.2 years. All participants were right-handed. Nine participants were male, and one was female.

Statistical analysis of accuracy and time data was performed using paired t-tests, with significance levels set at $p<0.05$ and $p<0.01$, respectively. A sensitivity analysis was performed to account for up to 1 mm error in distance measurements during image analysis by adding 1 mm to measured distance between participant mark using the AR face filter and expert botulinum practitioner mark. Survey data was analysed using Friedman's test and if significance found, post-hoc analysis with Wilcoxon signed-rank tests and Bonferroni correction was applied.

RESULTS

Accuracy

Participants were more accurate with the smartphone app than with the diagram, with average distance from expert-identified location 4.6 mm versus 6.8 mm, respectively, and this difference was statistically significant ($p<0.01$ [Figure 2A]). When data was analysed by distribution of the injection site locations, participants were more accurate with the app versus the anatomy diagram when identifying injection locations on the lateral aspect of the face (5.4 mm versus 8.4 mm, respectively; $p<0.01$ [Figure 2B]). Accuracy was also greater with

Table 1: Injection site anatomical labels.

Injection site	Medial sites	Lateral sites
1	Right depressor supercilii and corrugator supercilii	N/A
2	Left depressor supercilii and corrugator supercilii	N/A
3	Right inferomedial orbicularis oculi	N/A
4	Left inferomedial orbicularis oculi	N/A
5	N/A	Left superolateral orbicularis oculi muscle
6	N/A	Left inferolateral orbicularis oculi muscle
7	N/A	Left lateral zygomaticus muscle
8	N/A	Right superolateral orbicularis oculi muscle
9	N/A	Right inferolateral orbicularis oculi muscle
10	N/A	Right lateral zygomaticus muscle

N/A: not applicable.

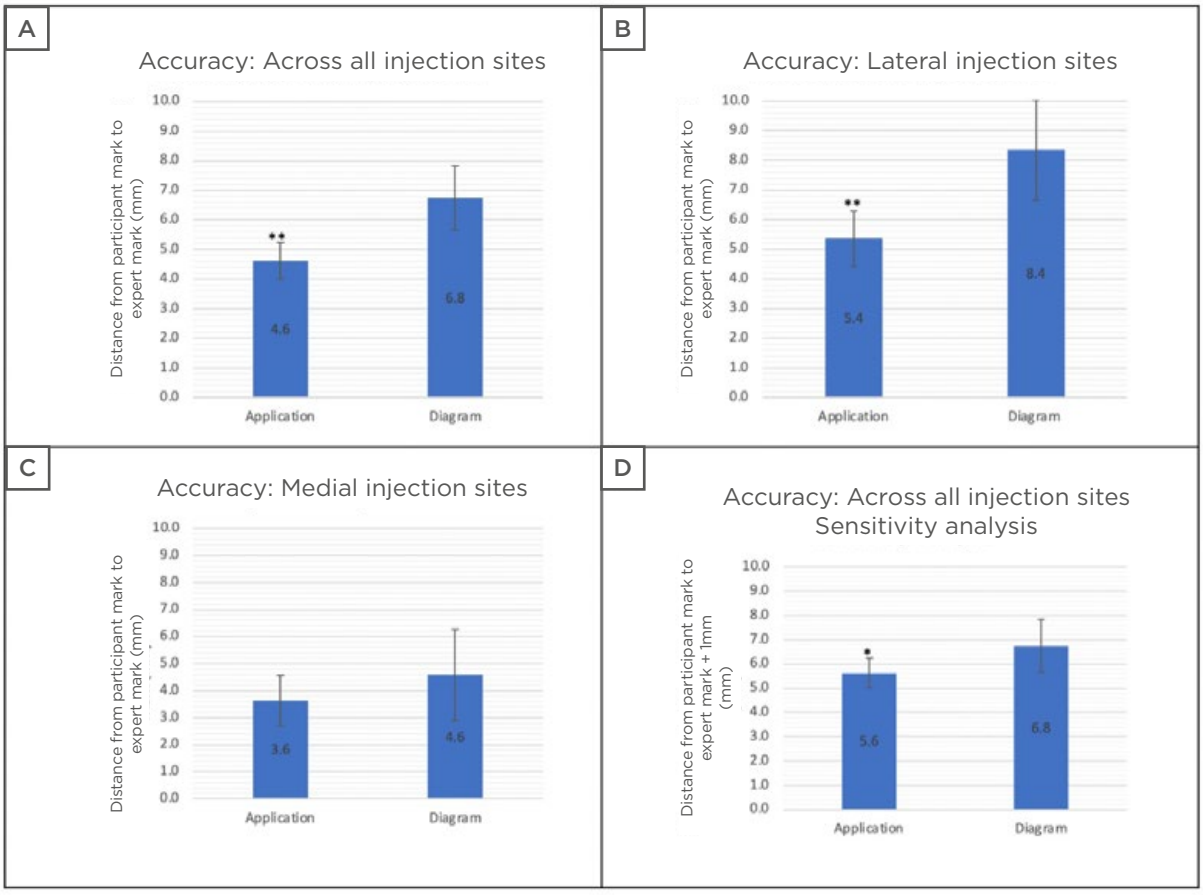

Figure 2: Assessment of mean accuracy using the app versus the anatomy diagram. Error bars denote 95% confidence interval (*p<0.05, **p<0.01).

A) Accuracy across all injection sites using the app versus the anatomy diagram (p<0.01). **B)** Accuracy for lateral injection sites using the app versus the anatomy diagram (p<0.01). **C)** Accuracy for medial injection sites using the app versus the anatomy diagram. No significant difference was demonstrated. **D)** Accuracy using the app versus the anatomy diagram. Sensitivity analysis performed to account for up to 1 mm error during image analysis. Error bars denote 95% confidence intervals (p<0.05).

the app than with the anatomy diagram when identifying injection sites on the medial aspect of the face, although this difference did not meet statistical significance (3.6 mm versus 4.6 mm; p=0.07 [Figure 2C]).

Among individual points, participants were only significantly more accurate with the app than the diagram in identifying sites 2 (3.4 mm versus 5.4 mm; p<0.05), 7 (6.6 mm versus 13.6 mm; p<0.05), and 8 (4.3 mm versus 8.7 mm; p<0.05). Differences in accuracy with use of the app versus the diagram did not meet statistical significance for all other points.

After sensitivity analysis accounting for 1 mm error during image analysis, accuracy remained significantly higher with use of the app versus the diagram (5.6 mm versus 6.8 mm respectively; p<0.05 [Figure 2D]).

Time

Time taken to mark all 10 injection sites on the face of the test subject was available for eight participants. Participants took significantly longer to complete the task when using the app versus the anatomy diagram (79.8 versus 57.8 seconds; p<0.01).

Survey

Confidence

There was a statistically significant difference in participants' confidence in identifying injection sites among participants before the task, using

the app, and using the anatomy diagram, $\chi^2(2)=8.970$; p=<0.05. Post-hoc analysis with Wilcoxon signed-rank tests was conducted and Bonferroni correction applied. Median (interquartile range [IQR]) for confidence levels in identifying injection sites before the task, using the app, and using the anatomy diagram were 0.00 (0.00–2.25), 5.50 (3.00–8.00), and 6.00 (2.75–6.25), respectively, and significance level was set at p<0.017. Participants demonstrated a statistically significant increase in confidence levels when using the app compared with their confidence levels prior to the task (Z=-2.395; p<0.05) and a statistically significant increase in confidence levels when using the diagram compared with their confidence levels prior to the task (Z=-2.530; p<0.05). However, there was no significant difference between participants' confidence levels using the app versus using the anatomy diagram (Z=-0.852; p=0.394).

Usefulness and perceived accuracy

There was no statistically significant difference in participants perceived usefulness of the app alone, anatomy diagram alone, nor app and anatomy diagram combined, as tools for identifying botulinum toxin injection sites $\chi^2(2)=1.067$; p=0.587. Median (IQR) for participants' perceived usefulness in identifying injection sites using the app, using the anatomy diagram, and both adjuncts together were 6.00 (4.75–7.25), 6.00 (4.75–6.25), and 6.00 (5.00–8.25), respectively.

There was no statistically significant difference in participants perceived accuracy using the app versus the anatomy diagram $\chi^2(2)=0.000$; p=1.000. Median (IQR) for participants' perceived accuracy using the app and using the anatomy diagram were 5.50 (3.00–8.00) and 5.00 (3.75–6.25), respectively.

Participant comments

Of the participants, 70% reported they were willing to use the app to guide them if they were to perform real botulinum toxin injections. Despite this, a number of participants stated they preferred using the diagram as an aid.

Participants reported two significant issues that caused movement of the face filter when using the app: difficulty in holding the supporting device still; and adjustment of the image frame when a participant's hand moved into view of the camera during marking of an injection site. These frame shifts were particularly apparent when marking injection sites on the side opposite to a participant's dominant hand and contributed to time delays in marking injection sites when using the app.

DISCUSSION

In this study, an AR face filter of facial muscles was developed by repurposing readily available software that is used recreationally to make social media face filters. This AR face filter allowed users to identify sites for facial botulinum toxin injection significantly more accurately than through traditional means of using a reference anatomy diagram. This improvement in accuracy is important in facial injection of botulinum toxin as it may minimise risk of side effects for patients. The results also demonstrate the potential of this readily available technology both as a learning tool and as a clinical aide for practitioners with limited experience.

Despite improvements in accuracy, participants were slower and no more confident in their performance when using the AR app compared with the anatomy diagram. Participants attributed this to difficulties in keeping the supporting device still, resulting in small but notable movements of the face filter. In the future, these concerns could be addressed by using hands-free devices or stands to keep the device camera stable. Specially designed head-mounted displays, or 'smart glasses', have already been trialled with success in neurosurgery[11] and maxillofacial surgery,[12] and the app-supporting headset Microsoft HoloLens (Microsoft Corporation, Redmond, Washington, USA) is being applied in multiple healthcare settings, including facilitating virtual ward rounds[13] as well as AR-assisted surgery.[14,15] A similar approach may therefore show benefit in botulinum toxin facial injections.

Over the previous decade, research into the use of AR within medicine has become increasingly prevalent. AR has predominantly been used to facilitate imaging-guided surgery by enabling pre-operative CT or MRI images to be overlain onto the surgical field and guide an operation in the context of the patient's real anatomy.[16]

This technology has been trialled in areas of the body that are generally non-deformable as manipulation of these tissues during surgery is minimal, requiring less processing power to track anatomy and maintain accurate image overlay. Consequently, AR research has focused on maxillofacial surgery,[12,17,18] neurosurgery,[11,19-22] orthopaedic surgery,[15,23,24] and hepatobiliary and pancreatic surgery.[25-29]

In contrast, this preliminary study suggests that AR has the potential to be harnessed in clinical domains without the need for prior imaging of the test subject. Here, facial recognition software designed for social media purposes was used to detect facial landmarks and allowed the filter of facial muscles to be overlaid, such that the resultant AR image forms an accurate representation of the test subject's underlying musculature. This technology can be relied upon further as facial recognition systems are becoming increasingly more accurate. In 2020, the best face identification algorithm had an error rate of 0.08%, compared to 4.10% for the leading algorithm in 2014.[30] In a recent study, a dedicated AR guide for botulinum toxin injection was developed by combining facial recognition software with a standard oral maxillofacial model based on CT or MRI images of patients.[9] With this guide, a mean accuracy of 0.40±0.25 mm was demonstrated with a range of 0–3 mm, a standard the authors deemed sufficient for use in clinical practice.[9]

AR filters must clearly achieve a higher standard of accuracy for use in clinical practice than for recreational use. With an average accuracy of 4.6 mm, the AR app used in this study does not meet the 3.0 mm error margin proposed as the limit suitable for clinical practice.[9] However, this preliminary study is the first to suggest that readily available software, designed for recreational social media purposes, can be harnessed to improve the accuracy of facial botulinum toxin injection when compared to the use of a standard anatomy diagram.

The study's findings are limited by its small sample size. While the results provide an encouraging basis for future research into use of AR for improvement of facial injection accuracy, the study is not adequately powered to draw definitive conclusions. Further research would involve using a larger cohort of participants as well as test subjects of different ages and genders to examine the reliability of the AR app. The 'gold standard' reference injection sites could also be refined by averaging opinions from multiple experienced botulinum practitioners, instead of the single expert consulted in this study.

CONCLUSION

As face filters and facial recognition technology are refined for entertainment and recreational purposes on social media, it is only a matter of time before this AR technology is routinely used in medical practice. In this preliminary study, participants were more accurate using an AR face filter app, developed using popular social media software, than they were with a traditional anatomy diagram. While participants did not perceive the app to be any better than the diagram, the improved accuracy using the app demonstrates a clear benefit. It is evident that this technology opens a promising avenue for not only training purposes, but with refinement and further advances, it has the potential to improve the accuracy of facial injections and reduce rates of complication in clinical practice. Further research is needed in optimising this technology prior to trialling its use in patients; however, AR seems to be a viable and useful adjunct for procedures requiring anatomy knowledge of the facial muscles.

References

1. Kao I et al. Botulinum toxin: mechanism of presynaptic blockade. Science. 1976;193(4259):1256-8.
2. Blasi J et al. Botulinum neurotoxin A selectively cleaves the synaptic protein SNAP-25. Nature. 1993;365(6442):160-3.
3. Münchau A, Bhatia KP. Uses of botulinum toxin injection in medicine today. BMJ. 2000;320(7228):161-5.
4. Nigam PK, Nigam A. Botulinum toxin. Indian J Dermatol. 2010;55(1):8-14.
5. Small R. Botulinum toxin injection for facial wrinkles. Am Fam Physician. 2014;90(3):168-75.
6. Raffaela P et al., "Botulinum toxin adverse events," Serdev N (ed.), Botulinum Toxin (2018), 1st edition, London: IntechOpen, pp.33-6.
7. Kemp S. Digital 2021 April global statshot report. 2021. Available at:

https://datareportal.com/reports/digital-2021-april-global-statshot. Last accessed: 18 November 2021.

8. Shaburova E; United States Patent Application Publication. Method for real time video processing for changing proportions of an object in the video. 2015. Available at: https://patentimages.storage.googleapis.com/6d/f0/58/aaca29a68d77b5/US20150222821A1.pdf. Last accessed: 18 November 2021.
9. Kim HJ et al. Augmented reality for botulinum toxin injection. Concurr Comput. 2020;DOI:10.1002/cpe.5526.
10. Spark AR Studio. Available at: https://sparkar.facebook.com/ar-studio/. Last accessed: 18 November 2021.
11. Tabrizi LB, Mahvash M. Augmented reality-guided neurosurgery: accuracy and intraoperative application of an image projection technique. J Neurosurg. 2015;123(1):206-11.
12. Badiali G et al. Augmented reality as an aid in maxillofacial surgery: validation of a wearable system allowing maxillary repositioning. J Craniomaxillofac Surg. 2014;42(8):1970-6.
13. Microsoft. Imperial College Healthcare NHS Trust uses mixed reality in the fight against COVID-19. 2020. Available at: https://customers.microsoft.com/en-us/story/825289-imperial-nhs. Last accessed: 18 November 2021.
14. Microsoft. A hospital revolution: 3D assistance in operations. 2019. Available at: https://customers.microsoft.com/en-us/story/770890-apoqlar-azure-hololens-cognitive-services-health-en. Last accessed: 18 November 2021.
15. Dennler C et al. Augmented reality in the operating room: a clinical feasibility study. BMC Musculoskelet Disord. 2021;22(1):451.
16. Fida B et al. Augmented reality in open surgery. Updates Surg. 2018;70(3):389-400.
17. Qu M et al. Precise positioning of an intraoral distractor using augmented reality in patients with hemifacial microsomia. J Craniomaxillofac Surg. 2015;43(1):106-12.
18. Cercenelli L et al. The wearable VOSTARS system for augmented reality-guided surgery: preclinical phantom evaluation for high-precision maxillofacial tasks. J Clin Med. 2020;9(11):3562.
19. Cabrilo I et al. Augmented reality-assisted skull base surgery. Neurochirurgie. 2014;60(6):304-6.
20. Watanabe E et al. The trans-visible navigator: a see-through neuronavigation system using augmented reality. World Neurosurg. 2016;87:399-405.
21. Kersten-Oertel M et al. Augmented reality in neurovascular surgery: feasibility and first uses in the operating room. Int J Comput Assist Radiol Surg. 2015;10(11):1823-36.
22. Haemmerli J et al. Evaluation of the precision of operative augmented reality compared to standard neuronavigation using a 3D-printed skull. Neurosurg Focus. 2021;50(1):E17.
23. Keating TC, Jacobs JJ. Augmented reality in orthopedic practice and education. Orthop Clin North Am. 2021;52(1):15-26.
24. Molina CA et al. Augmented reality-assisted pedicle screw insertion: a cadaveric proof-of-concept study. J Neurosurg Spine. 2019;33(1):139-46. Erratum in: J Neurosurg Spine. 2020;120(1):120.
25. Pessaux P et al. Towards cybernetic surgery: robotic and augmented reality-assisted liver segmentectomy. Langenbecks Arch Surg. 2015;400(3):381-5.
26. Golse N et al. Augmented reality during open liver surgery using a markerless non-rigid registration system. J Gastrointest Surg. 2021;25(3):662-71.
27. Okamoto T et al. Navigation surgery using an augmented reality for pancreatectomy. Dig Surg. 2015;32(2):117-23.
28. Luo H et al. Augmented reality navigation for liver resection with a stereoscopic laparoscope. Comput Methods Programs Biomed. 2020;187:105099.
29. Tang R et al. Augmented reality-assisted pancreaticoduodenectomy with superior mesenteric vein resection and reconstruction. Gastroenterol Res Pract. 2021;DOI:10.1155/2021/9621323.
30. Grother P et al.; National Institute of Standards and Technology (NIST) US Department of Commerce. Face recognition vendor test (FRVT): part 2: identification. 2019. Available at: https://nvlpubs.nist.gov/nistpubs/ir/2019/NIST.IR.8271.pdf. Last accessed: 18 November 2021.

The Evolving Evidence Base of Implantable Cardiac Defibrillators: Past, Present, and Future

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Abstract

This review describes the evidence that forms the foundation for the use of an implantable cardiac defibrillator (ICD). The authors present the current guidelines for the implantation of ICDs and describe the most important historic and latest clinical trials that have been conducted to examine the role of ICDs for primary and secondary prevention of a cardiac arrest. Finally, the authors discuss new technologies that have been developed to improve outcomes and reduce adverse events associated with these types of cardiac implantable electronic devices.

INTRODUCTION

Since its first clinical use in 1980,[1] implantable cardiac defibrillators (ICD) have become a standard tool in the treatment of heart failure (HF) and prevention of sudden cardiac death (SCD) in patients fortunate enough to have survived a cardiac arrest. Cardiologists are commonly faced with the decision of whether to refer patients for ICD implantation based on the individual patient characteristics and best available evidence. This review aims to reflect on the evolving evidence about ICDs from pivotal clinical trials that have shaped and expanded its indication in modern cardiology. The authors will also explore the emerging role of subcutaneous ICD (S-ICD) as an alternative to the conventional ICD device.

Current Guideline Recommendation

The latest European Society of Cardiology (ESC) guidelines on HF promote the implantation of ICD not only in patients who survived a cardiac arrest caused by a ventricular arrhythmia (i.e., secondary prevention), but also in patients classified as at high risk of SCD (i.e., primary prevention). Besides channelopathies and congenital heart disease, primary prevention primarily involves patients with significant left ventricular systolic dysfunction, left ventricular ejection fraction (LVEF) ≤35% due to ischaemic (ICM) or non-ischaemic cardiomyopathy (NICM) with New York Heart Association (NYHA) Class II–III symptoms despite optimal medical therapy (OMT) for >3 months and a life expectancy of >1 year.[2]

Historical Evidence for Secondary Prevention

The guidance on secondary prevention was instigated by the historic AVID[3] and CASH[4] trials, which began recruitment in the late 1980s. Although these trials were conducted over two decades ago when HF treatments were limited to ß-blockers and angiotensin-converter enzyme inhibitors, they provided a strong foundation for the prognostic benefits of ICD in patients with unstable ventricular arrhythmia or survivors of cardiac arrest. CASH and AVID found a 20% and 39% relative risk reduction of mortality, respectively.[3,4] At the beginning of CASH, ICDs were still epicardial systems which were implanted by cardiothoracic surgeons via thoracotomy. Over the course of the trial, miniaturisation and development of endocardial leads revolutionised the approach and implantation of transvenous ICD (TV-ICD) as we know today.

Primary Prevention Implantable Cardioverter Defibrillator for Ischaemic Cardiomyopathy

The basis for the recommendation of preventative ICD for patients who have never experienced a life-threatening arrhythmia or cardiac arrest is more elaborate. Initial trials were largely based on patients considered at high risk for life-threatening arrhythmias. Published in 1996, MADIT 1 recruited 196 patients with a previous myocardial infarction (MI) and LVEF ≤35%. Compared to the OMT cohort, there was a 54% reduction of all-cause mortality in the defibrillator-treated group (p=0.009). However, this study population not only had to have documented evidence of previous ventricular tachycardia (VT) but also had to undergo an electrophysiology study to elicit VT.[5] The study findings were corroborated in the larger MUSTT trial.[6] Similarly, patients were selected on the basis of an episode of asymptomatic non-sustained VT at least 4 days post-MI with evidence of inducible VT on electrophysiology study in the intervention arm, but with a slightly less stringent LVEF of ≤40%. In a three-arm design, it found that electrophysiology (EP)-guided therapy with a defibrillator resulted in a 50% reduction in total mortality and a 70% reduction in arrhythmic death, compared to patients assigned to either EP-guided medical therapy or no antiarrhythmic therapy.[6]

The MADIT II trial, published in 2002, took a practical stance and obviated the need for EP testing before enrolment.[7] In a similar population of patients post-MI with systolic dysfunction (LVEF: ≤30%), prophylactic ICD was found to improve survival, with a 31% relative risk reduction in all-cause mortality compared to medical therapy only (hazard ratio [HR]: 0.69, p=0.016). However, like the preceding studies, it excluded patients with recent MIs within the last month. To address this gap, DINAMIT, published 2 years later, enrolled patients with an MI between 6 and 40 days earlier, LVEF ≤35%, and impaired cardiac autonomic function.[8] No clinical benefit was found in patients with a recent MI; this was subsequently reflected in the ESC guidelines.[2]

TRANSLATION OF EVIDENCE TO NON-ISCHAEMIC CARDIOMYOPATHY

While evidence of ICD for ICM accumulated, investigators recognised the need to explore the same for patients with NICM. The SCD-HeFT trial was sufficiently powered to examine this.[9] Over 2,500 patients with severe left ventricular systolic dysfunction and an equal distribution of ICM and NICM were randomised to either ICD, amiodarone, or placebo. At 4 years follow-up, ICD therapy significantly reduced all-cause mortality for both NICM and ICM compared to the other arms (HR: 0.77, p=0.007). That said, in a subgroup analysis of NICM alone (n=792), only a non-significant trend towards reduced mortality was found (HR: 0.73; 97.5% confidence interval [CI]: 0.50–1.07).[9]

A comparable study population of patients with ICM and NICM was recruited in the COMPANION trial but for the first time, patients had to have a QRS prolongation (>120 msec) to study the effects of cardiac resynchronisation therapy (CRT) on a composite primary endpoint of all-cause mortality and hospitalisation. Randomised to three arms of OMT, OMT plus biventricular pacing, and OMT plus biventricular defibrillator (CRT-D), the study was halted early due to demonstration of superior efficacy in both resynchronisation arms on its primary outcome (HR: 0.81,

p=0.015). Furthermore, it was noted that CRT-D had a greater effect on all-cause mortality than CRT alone, galvanising studies to explore this further.[10]

Cardiac Resynchronisation Therapy

Is the degree of QRS prolongation a target to improve mortality? The MADIT-CRT trial began recruitment in 2004:[11] 1,820 patients with NICM and ICM, LVEF ≤30% but with milder HF symptoms (NYHA I–II), and a QRS duration ≥130 msec were randomised to receive either a biventricular defibrillator or an ICD alone. Primary outcome was death from any cause or non-fatal HF events. At 2.5 years follow-up, there was a 30% relative risk reduction in the primary endpoint in the biventricular defibrillator group compared to ICD alone (HR: 0.66; 95% CI: 0.52–0.84; p=0.001).[11] This provided convincing evidence that preventive CRT-D reduces HF events in patients with either ICM or NICM with a wide QRS complex and relatively well-controlled HF symptoms. In a subgroup analysis of patients with left bundle branch block (LBBB), the primary outcome was even more pronounced (HR: 0.43; 95% CI: 0.33–0.56; p<0.001) while non-LBBB demonstrated less improvement of LVEF with no significant reduction in SCD.[12] Based on MADIT-CRT and COMPANION, it is now a Class I recommendation to offer a biventricular defibrillator rather than conventional ICD to patients with chronic HF, LVEF ≤35%, and at least NYHA Class II with LBBB and QRS duration ≥130 msec.[2]

While the Echo-CRT trial was stopped early for futility and possible harm of CRT in patients with HF with reduced ejection fraction (HFrEF) with narrow QRS complexes (<130 msec),[13] there are specific patient populations that may prognostically benefit from CRT despite a narrow QRS duration. Apart from patients with HFrEF who require chronic right ventricular pacing for bradyarrhythmia,[14] one such population was highlighted in the recent APAF-CRT trial, which was stopped early for efficacy of its 'ablate and pace' strategy in narrow-QRS HF.[15] In this open-label trial, 133 patients (mean age: 73±10 years) with severely symptomatic permanent atrial fibrillation and at least one HF hospitalisation in the last year were randomly assigned to either atrioventricular junction ablation plus CRT or pharmacological rate control. The primary endpoint was all-cause mortality. After a median 29 months follow-up, the former intervention was associated with a substantial 74% reduction in death (HR: 0.26; 95% CI: 0.10–0.65; p=0.004) with no significant differences in benefit between patients with LVEF below or above 35%. The number needed to treat to prevent one event was 3.7.[15] From this, there is a suggestion of additional benefit in CRT for patients who are candidates for atrioventricular junction ablation to optimise atrial fibrillation rate control in patients with HF and narrow QRS. Nonetheless, a large sample size is required before confidently adopting this approach.

The Role of Implantable Cardioverter Defibrillators in a Modern Era of Guideline-Directed Therapies

Guideline-directed medical therapies for HFrEF have progressed. The arrival of sacubitril/valsartan and sodium-glucose cotransporter-2 inhibitors (SGLT2i) have demonstrated strong mortality benefits in this patient group.[16,17] With this in mind, will the efficacy of ICD in preventing SCD remain despite a greater armamentarium of HF drugs? Trials comparing biventricular defibrillators versus biventricular pacemakers in patients eligible for primary prevention ICD will hopefully shed light on this.[18]

Partially addressing this question for the NICM population is the DANISH trial, published 5 years ago. Recognising the gradual reduction of SCD rates over the last 20 years with greater uptake of HF pharmacotherapies, it recruited the largest population of patients with NICM (N=556) with LVEF ≤35% to examine the mortality benefits of ICD. Over 67.6 months, all-cause mortality was no different between the ICD versus control group (HR: 0.87; 95% CI: 0.68–1.12; p=0.28). More importantly, its overall rate of SCD was much lower than previous trials, and this trend is likely to continue since the advent of sacubitril/valsartan and SGLT2i, which were unavailable during DANISH.[19]

As summarised in Table 1 of the above clinical trials, it took the last 25 years to collect evidence that patients with ICM and LVEF

Table 1: Summary of major clinical trials of implantable cardioverter defibrillators.

Year	Study	Indication	Patients (N)	Study population	Results
1996	MADIT[5]	Primary	196	Ischaemic CM; LVEF: ≤35%; NYHA: I–III; asymptomatic NSVT or inducible VT on EPS	54% relative risk reduction in mortality with ICD
1997	AVID[3]	Secondary	1,013	Symptomatic VT; survivors of SCD; LVEF: ≤40%	31% relative risk reduction in mortality with ICD at 3 years
1999	MUSTT[6]	Primary	704	Ischaemic CM; LVEF: <40%; asymptomatic NSVT	51% relative risk reduction in mortality with ICD
2000	CASH[4]	Secondary	288	SCD survivors, unstable VT	23% relative risk reduction in mortality with ICD
2002	MADIT-II[7]	Primary	1,232	Ischaemic CM: LVEF: <30%; more than 30 days from onset of myocardial infarction	31% relative risk reduction in mortality with ICD
2004	DEFINITE[20]	Primary	458	Non-ischaemic CM (DCM); LVEF ≤35% NSVT or premature ventricular complexes (≥10 beats/hour) on Holter	ICD reduced rate of death from any cause (7.9% versus 14% at 2 years)
2004	DINAMIT[8]	Primary	674	Ischaemic CM, recent MI within 4–40 days; LVEF: ≤35%; impaired HR variability	No reduction in all-cause death with ICD therapy (p=0.66) but reduction in arrhythmic deaths (p=0.009)
2004	COMPANION[10]	Primary	1,520	Ischaemic and non-ischaemic CM; NYHA: III–IV; LVEF QRS: >120 msec	Approximately 20% reduction in composite of all-cause hospitalisation or death with CRT
2005	SCD-HeFT[9]	Primary	2,521	Ischaemic and non-ischaemic CM; LVEF: <35%; NYHA: II–III	23% relative risk reduction in mortality with ICD
2016	DANISH[19]	Primary	1,116	Non-ischaemic CM; LVEF: ≤35; NYHA: II–III (IV if for CRT); optimal medical therapy, including CRT	No mortality reduction with ICD 3% absolute reduction in SCD mitigated by 1.5% absolute risk of device-related infection

CM: cardiomyopathy; CRT: cardiac resynchronisation therapy; DCM: dilated cardiomyopathy; EPS: electrophysiology study; HR: heart rate; ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction; NSVT: non-sustained ventricular tachycardia; NYHA: New York Heart Association; SCD: sudden cardiac death; VT: ventricular tachycardia.

≤35% benefit from ICD implantation, and do even better when treated with a biventricular defibrillator if the QRS duration is prolonged. On the other hand, patients with NICM seem not to benefit from a defibrillator on the whole.

Subcutaneous Versus Transvenous Implantable Cardioverter Defibrillator

Another point highlighted by DANISH was the substantial complication rate in the ICD group,

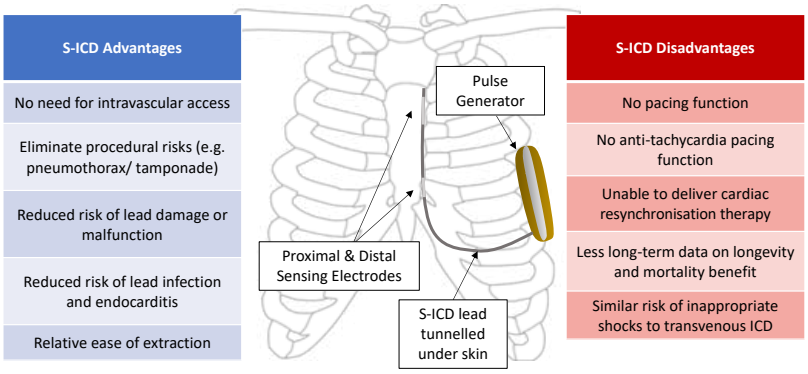

Figure 1: Position of subcutaneous implantable cardiverter defibrillator and its advantages and disadvantages.

ICD: implantable cardioverter defibrillator; S-ICD: subcutaneous implantable cardioverter defibrillator.

offsetting the 3% reduction in mortality; 3% of patients had a serious device-related infection, 2% experienced pneumothorax, and 6% received inappropriate shocks (IAS).[19] The inherent risks associated with the implantation of TV-ICDs may be circumvented by the pioneering technology of subcutaneously implanted defibrillators. As illustrated in Figure 1, the S-ICD lead is tunnelled subcutaneously on top of the rib cage cranially towards the suprasternal notch. The distal sensing electrode is placed adjacent to the manubriosternal notch and the proximal sensing electrode near the xiphoid process. The extra-thoracic device lies on the left thoracic region, close enough to the heart to sense the far-field ECG and terminate any life-threatening ventricular arrhythmia.[21]

Based on the pros and cons of S-ICD (Figure 1), it is usually recommended in younger patients, those with a history of vascular access problems, or those considered to be at high risk for device-related infections. By virtue of its design, S-ICD would not be appropriate in patients who require bradycardia pacing, CRT, or a need for anti-tachycardia pacing. Furthermore, due to its reliance on far-field sensing as opposed to near-field electrograms detected by TV-ICD, the risk of IAS from cardiac oversensing was relatively higher.[22,23] Software and hardware modifications over the last 10 years have improved this. One key development is the SMART-PASS filtering algorithm, which lowers the T-wave amplitude in order to minimise the risk of IAS from T-wave oversensing.[24]

The potential to combine S-ICD with a leadless pacemaker is another attractive solution to utilise the benefits of both systems of a less invasive defibrillator while providing anti-tachycardia pacing delivery and pacing.

Although S-ICD has been approved for use in Europe over the last 10 years,[21] its evidence base is still in its infancy compared with TV-ICD. PRAETORIAN is the first randomised trial comparing subcutaneous versus transvenous defibrillators.[25] The trial was designed and powered as a non-inferiority trial with a safety primary composite endpoint of device-related complications and IAS.

Researchers recruited 849 patients who had an indication for ICD but not for pacing. At a median follow-up of 49.1 months, there was no significant difference in primary outcome (HR: 0.99; 95% CI: 0.71–1.39; p=0.01 for non-inferiority). This suggested that in the absence of the need for pacing or resynchronisation, S-ICD appeared non-inferior to TV-ICD. It is important to note that the high-pass filter function for S-ICD was unavailable in >75% of cases since PRAETORIAN began, and hence the risk of IAS may be lower than observed.[25]

Hopefully, a clearer picture of the differences between S-ICD and TV-ICD will be known as the trial continues for a further 4 years.

REDUCING THE RISK OF INAPPROPRIATE SHOCKS FROM SUBCUTANEOUS IMPLANTABLE CARDIOVERTER DEFIBRILLATORS

Even now, we can already see how far technology has progressed with S-ICDs in reducing IAS. From the first large real-world data on S-ICD in EFFORTLESS,[22,23] a high IAS rate of 8.1% was reported. This is lower than that observed with earlier TV-ICD in the era of MADIT-II and SCD-HeFT where an IAS rate between 13% and 17% was described.[7,9] Obviously, device programming has advanced since then. PRAETORIAN revealed an IAS rate of 4.1% with TV-ICD versus 4.9% for S-ICD.[25] An even lower rate of 2.5% was found in the recent UNTOUCHED study, which employed contemporary electrogram filtering and algorithms.[26] These modern devices not only had SMART-PASS filtering but were also programmed with a conditional zone of 200 bpm (using beat-to-beat and QRS width analyses) to differentiate supraventricular from ventricular arrhythmias and shock zone of 250 bpm.[26]

Clinical Implication

This review highlights the constantly shifting landscape of ICD implantation, dictated by its dynamic and developing evidence base. Emphasised in the latest 2021 ESC guidelines for the management of chronic HF[27] and use of CRT,[14] an important clinical implication is the careful selection of patients and multi-disciplinary involvement before pursuing primary prevention ICD implantation. Recommendation for primary preventative ICD in the NICM population (based on the same indications as ICM) has been downgraded to Class IIa in light of the DANISH trial and a meta-analysis.[19,27,28] The falling burden of SCD and cardiovascular mortality in the NICM population attributed to the use of contemporary HF therapy makes it difficult for ICDs to further reduce the risk of SCD. That said, with careful patient selection, young patients with little comorbidity may still benefit. Another area where careful patient selection is key is the use of S-ICD. When used in appropriately selected patient groups, it can be used as a non-inferior alternative in safety and efficacy to TV-ICDs.[14,27]

CONCLUSION

We have come a long way since the first clinical use of ICD in the early 1980s. The advances of ICD technology have made it safer and effective to prevent SCD and treat HF in both ICM and NICM. It has resulted in a striking global increase in the implantation of defibrillators and resynchronisation devices with its indications continually being redefined and expanded by ongoing research. S-ICDs have provided a valuable alternative to the transvenous type, which is implanted on an individualistic approach and continues to evolve to overcome its current shortcomings.

References

1. Mirowski M et al. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. N Engl J Med. 1980;303(6):322-4.
2. Ponikowski P et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200.
3. Antiarrhythmics versus implantable defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med. 1997;337(22):1576-83.
4. Kuck KH et al. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). Circulation. 2000;102(7):748-54.
5. Moss AJ et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med. 1996;335(26):1933-40.
6. Buxton AE et al. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med. 2000;342(26):1937-45.
7. Moss AJ et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002;346(12):877-83.
8. Hohnloser SH et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med. 2004;351(24):2481-8.
9. Bardy GH et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352(3):225-37.
10. Bristow MR et al. Cardiac-resynchronization therapy with or

without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004;350(21):2140-50.

11. Moss AJ et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med. 2009;361(14):1329-38.
12. Zareba W et al. Effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). Circulation. 2011;123(10):1061-72.
13. Ruschitzka F et al. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. N Engl J Med. 2013;369(15):1395-405.
14. Glikson M et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J. 2021;42(35):3427-520.
15. Brignole M et al. AV junction ablation and cardiac resynchronization for patients with permanent atrial fibrillation and narrow QRS: the APAF-CRT mortality trial. Eur Heart J. 2021;ehab569.
16. McMurray JJV et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995-2008.
17. McMurray JJ et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993-1004.
18. Leipzig Heart Institute GmbH. Re-evaluation of optimal re-synchronisation therapy in patients with chronic heart failure (RESET-CRT). NCT03494933. https://clinicaltrials.gov/ct2/show/NCT03494933.
19. Køber L et al. Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med. 2016;375(13):1221-30.
20. Kadish A et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med. 2004;350(21):2151-8.
21. Bardy GH et al. An entirely subcutaneous implantable cardioverter-defibrillator. N Engl J Med. 2010;363(1):36-44.
22. Lambiase PD et al. Worldwide experience with a totally subcutaneous implantable defibrillator: early results from the EFFORTLESS S-ICD Registry. Eur Heart J. 2014;35(25):1657-65.
23. Boersma L et al. Implant and midterm outcomes of the subcutaneous implantable cardioverter-defibrillator registry: the EFFORTLESS study. J Am Coll Cardiol. 2017;70(7):830-41.
24. Theuns DAMJ et al. Prospective blinded evaluation of a novel sensing methodology designed to reduce inappropriate shocks by the subcutaneous implantable cardioverter-defibrillator. Heart Rhythm. 2018;15(10):1515-22.
25. Knops RE et al. Subcutaneous or transvenous defibrillator therapy. N Engl J Med. 2020;383(6):526-36.
26. Gold MR et al. Primary results from the understanding outcomes with the S-ICD in primary prevention patients with low ejection fraction (UNTOUCHED) trial. Circulation. 2021;143(1):7-17.
27. McDonagh TA et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599-726.
28. Beggs SAS et al. Non-ischaemic cardiomyopathy, sudden death and implantable defibrillators: a review and meta-analysis. Heart. 2018;104(2):144-50.

Current Therapy in Inflammatory Bowel Disease: Why and How We Need to Change?

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Abstract

During the last few decades, major progress has been made in the treatment of the two major forms of inflammatory bowel disease (IBD): Crohn's disease and ulcerative colitis. However, the success of the most advanced forms of therapy is at best 50%, and most patients lose responsiveness with time and need to switch to alternative medications. This denotes that a therapeutic ceiling has been reached and brand new approaches are badly needed. This commentary first briefly reviews current and recent therapeutic approaches for Crohn's disease and ulcerative colitis, pointing out their limitations. This is followed by an objective evidence-based discussion of why the current approaches are far from optimal, and the commentary is concluded by proposing how to change IBD treatment based on the holistic concept of network medicine, and how to implement precision medicine for IBD using artificial intelligence-based multi-omics analyses.

INTRODUCTION

Inflammatory bowel disease (IBD) represents a group of idiopathic chronic inflammatory disorders of the gastrointestinal tract, including Crohn's disease (CD), ulcerative colitis (UC), and IBD unspecified. The growing prevalence and significant impact of IBD around the world has made it the focus of decades of dedicated investigation, but the understanding of its pathogenesis has remained disappointingly elusive.[1] The so called 'hygiene hypothesis' has been proposed, based on the notion that increased industrialisation, better sanitation, and subsequent societal changes could explain the worldwide emergence of IBD.[2] However, the combined interplay of environmental, social, genetic, epigenetic, transcriptional, microbial, dietary, and immune factors that lead to the development of IBD and dictate its clinical course is poorly understood.[3]

Currently, the diagnosis of IBD is still made via expert assessment based on a combination of symptoms, laboratory parameters, stool testing, imaging, endoscopic, and histologic evaluation of the gastrointestinal tract.[4,5] The result of this traditional approach is not always straightforward. The diagnosis of IBD can be

delayed for years and, once made, may require reclassification into a different subcategory.[6] As many as 10% of patients diagnosed with UC ultimately end up being reclassified as CD, while 5% of those labelled with CD ultimately end up with their diagnosis being reclassified as UC.[7,8] This difficulty in classification is especially evident in patients who have undergone what was once touted as a curative colectomy for UC, followed by restorative pouch creation. In fact, as many as 40% of these patients go on to develop recurrent symptoms, and 10% are diagnosed with CD-like disease of the pouch, making the distinction between UC and CD more fluid than once thought.[9,10]

Regardless of IBD type, the clinical course is highly heterogeneous. Some patients have a benign course, some have relapsing disease, and some present with an aggressive phenotype complicated by strictures, fistulas, perianal disease, dysplasia, malignancy, and/or extra-intestinal manifestations.[11] As a result of this variability and diagnostic delay, many patients with IBD will have one or more of these complications prior to when therapy is initiated.[12]

Thus, considering all the above obstacles, it is not surprising that, despite the wide and growing number of therapeutic agents approved for UC or CD, therapeutic efficacy remains impossible to predict and regrettably modest.

CURRENT THERAPEUTIC PARADIGMS

Early Immunomodulators

The first drug accidentally shown to have a therapeutic effect in UC was salazopyrin (a salicylate compound) in the late 1940s.[13] Since that time, a number of 5-amino salicylic acid (5-ASA) formulations have been introduced in both oral and topical forms. The intestinal anti-inflammatory action of these agents is multifactorial and still poorly understood but is thought to be mediated via modulation of prostaglandin synthesis and suppression of pro-inflammatory cytokines.[14] Once the only therapeutic option for IBD, 5-ASA compounds are now recommended in a relatively small subset of patients with mild to moderate UC, but not in patients with severe UC or CD.[4,5]

Corticosteroids were the next agents to enter the IBD armamentarium. By binding cytoplasmic DNA receptors to inhibit DNA synthesis and tamp down the inflammatory response, they once became the mainstay of IBD therapy.[15] However, a solid body of evidence has established that corticosteroids are useful primarily for initiating but not maintaining remission, and display a number of side effects, ranging from metabolic derangements to psychiatric disturbances.[4,5] Budesonide, a steroid with some degree of intestinal specificity, has fewer side effects, but is still unable to maintain remission, and is less effective than systemic steroids.[16]

Drugs with immunomodulatory activity have been used for cancer treatment since the early 1960's, but their use for IBD started only after that of corticosteroids. Azathioprine and 6-mercaptopurine antagonise purine metabolism to deactivate T lymphocytes and suppress the immune system, but exhibit a long, delayed therapeutic action.[4,5,14] Only suitable as maintenance therapy, they are currently seldom used alone given their limited efficacy and substantial side effect profile, which includes dose-dependent myelosuppression, hepatotoxicity, rash, and malignancies, especially non-Hodgkin's lymphoma and non-melanomatous skin cancers.[4,5,17] Methotrexate, which blocks immune cell proliferation and induces immune cell apoptosis, is only useful in the induction and maintenance of remission of CD and is also seldom used alone.[4,18] Cyclosporine and tacrolimus are additional immunomodulators rarely used today due to modest efficacy and unfavourable collateral effects.

Antibiotics, Prebiotics, and Probiotics

During the 1980s and into the early 2000s, antibiotics became another mainstay of therapy. Many of them were tried, including rifaximin, clarithromycin, metronidazole, ciprofloxacin, amoxicillin, tetracyclines, vancomycin, and various combinations of these agents.[19] Although their use is theoretically justifiable, several randomised clinical trials showed trivial to minor benefits and no prolonged effect. Antibiotics are no longer routinely used in UC or CD except in selective clinical settings as, for example, therapy for pouchitis, adjunctive therapy for perianal CD, or prevention of post-operative CD recurrence, though research on the role of antibiotics in IBD is

still ongoing.[20] The use of prebiotics and probiotics is another area of ongoing research, especially given their favourable safety profile. These agents have shown some promise (especially VSL#3® [Alfasigma USA, Inc., Covington, Los Angeles, USA] in pouchitis), but studies are limited and have not yet convincingly demonstrated a robust benefit.[21,22]

Biologics

The current mainstay of IBD therapy is biological therapy, which is primarily based on monoclonal antibodies directed against specific molecules with immunomodulatory or inflammatory activity. Biologics are divided into four classes based on mechanism of action. The first and largest class of biologics are agents targeting TNF, a pro-inflammatory cytokine found in increased concentrations in the blood, stool, and colonic mucosa of patients with IBD.[23-25] Infliximab, the first of these agents, is administered intravenously and is used in patients with both UC and CD. Although infliximab revolutionised the care of patients with IBD and is among the ten highest grossing drugs in the USA, it maintains clinical remission in only 25% of patients with CD and 35% of patients with UC at 54 weeks.[26,27] Biosimilars targeting TNF have since been introduced and are of lower cost but still of similar efficacy.

Adalimumab, a successor of infliximab administered in a subcutaneous fashion, has similar remission rates of only 25% at Week 54 in patients with CD, and 17% at Week 52 in patients with UC.[28-30] Clinical trials with subsequent anti-TNF agents (golimumab, which has only been approved for UC; and certolizumab, which has been approved only for CD) did not fare much better, whether endpoints were clinical remission or mucosal healing.[31,32] To help overcome loss of response, anti-TNFs are often combined with immunomodulators, and therapeutic drug monitoring is being increasingly utilised, but even so many patients fail anti-TNF therapy.[33] In addition, these agents also carry side effects, ranging from infusion reactions, to opportunistic infections, to possible increased risk of malignancy, especially when used in combination with azathioprine.

A different type of biologic is the anti-leukocyte trafficking agent vedolizumab, engineered to block α4β7, an integrin mediating migration of immune cells from the peripheral blood into the intestinal tract.[14] Though this gut specificity makes for an improved side effect profile when compared to the anti-TNFs, remission rates are still limited, with 42% of patients with UC and 32% of patients with CD in remission at 52 weeks.[34,35]

Another type of biologic is ustekinumab, which targets the common p40 subunit of receptors for IL-12 and 23[14] cytokines, which induce the production of the cytokines interferon-γ and IL-17, respectively. This target was identified through genome-wide association studies and subsequently confirmed to be involved in CD pathogenesis.[14] However, overall ustekinumab-induced remission rate is still only around 53% in CD and 44% in UC at 52 weeks.[36,37] Its safety profile is comparable to that of vedolizumab.

Taken all together, response rates to biologics range anywhere from 20–50%.[38,39] When the high placebo response rates (anywhere from 7–30%) in drug trials are factored in, it becomes clear that, although a number of treatment options are now available, none can be considered a 'magic bullet'. In addition, even among initial responders, as many as 40% will lose response over time,[40] and those who lost response to one biologic agent are less likely to respond to a second. Moreover, despite biologics, around 11% of patients with UC will still require colectomy due to medically refractory disease, acute severe ulcerative colitis, mucosal dysplasia, or malignancy, and up to 70% of patients with CD will require surgery due to medically refractory disease, or complications that respond poorly to medical management.[41,42]

RECENT THERAPEUTIC PARADIGMS

New Agents and Combination Therapy

There are currently numerous new agents in Phase II and III clinical trials, including new monoclonal antibodies and new small molecules. Some of the new antibodies target the p19 subunit of the IL-23 receptor, with several agents under investigation, including risankizumab, brazikumab, and guselkumab.[43]

A number of small molecules have been developed that are either approved or under active investigation. These orally administered agents block JAKs, a family of pro-inflammatory enzymes that activate multiple immune pathways

instead of a single cytokine or receptor. The only JAK inhibitor presently approved is tofacitinib, but this agent is only effective in UC and response rates at 52 weeks are 34–41% depending on dosage, with a less favourable safety profile compared to vedolizumab or ustekinumab.[44,45] Other JAK inhibitors are under investigation and development and include upadacitinib, filgotinib, brepocitinib, peficitinib, TD-1473, and Pf-06651600/Pf-06700841, but it is unlikely that their therapeutic efficacy will be substantially better.[46] Another different type of small molecule under study is AVX-470, a new anti-TNF oral formulation.[47]

Inhibitors of lymphocyte trafficking agents with a mechanism of action similar to vedolizumab are also under investigation, such as abrilumab, etrolizumab, ontamalimumab, and AJM300.[45] In addition, one agent targeting leukocyte trafficking via sphingosine-1-phosphate, named ozanimod, was newly approved by the U.S. Food and Drug Administration (FDA) for UC, and other agents in this class are in Phase II and III trials.[48]

Given that all these agents are targeting similar pathways, the chance that any of them will have a significantly improved efficacy compared to available agents is low. In addition, real life effectiveness of all drugs on the market is extremely low, ranging from 5–13%,[49] so promise and potential are limited. Partly for these reasons, there is an emerging interest in combination therapy, in which two biologics with different mechanisms of action are combined. The field is still in its infancy, but early data suggest response rates remain at best around 50%.[50,51]

ALTERNATIVE AND COMPLEMENTARY APPROACHES

Looking at the history of IBD therapeutics, it is obvious that the immune system has been the single major focus of therapeutic interventions, even though IBD is a multifactorial disease. In fact, apart from the encouragement of smoking cessation, there has been a limited attention to any treatments that do not involve modulation of the immune system. Elemental diets have shown some promise, but are difficult for patients to tolerate.[52] There is also some evidence for benefits from exclusion diet (excluding wheat, dairy, emulsifiers, maltodextrins, carrageenans, and sulfites, and is low in animal fat), or a partial elemental diet (a free diet along with a minimum 900 kcal/day of elemental nutrition) in patients with CD.[52] Recently, stem cell therapies have also emerged as possible therapeutics for perianal CD, though the work is preliminary and response rates are thus far similar to that of biologics.[53] Finally, faecal microbial transplantation shows some promise, but it is still under study and has not convincingly emerged as a reliable treatment alternative.[54]

MEDICALLY REFRACTORY DISEASE

It is important to note that there are a number of specific clinical presentations of IBD, which will not respond well to any of the above therapies. Perianal and fistulising diseases almost always require surgical intervention, as does fibrostenotic disease. Once dysplasia and/or malignancy develops, the vast majority of patients will also require either advanced endoscopic or surgical interventions.

WHY TO CHANGE THE THERAPEUTIC APPROACH TO INFLAMMATORY BOWEL DISEASE

Taking all the above information into consideration and honestly judging how good current IBD therapies truly are, one must reach the obvious conclusion that they are not particularly effective. This brings up the existential issue of why IBD cannot be cured, and the answer is that IBD cannot be cured because 'life is complicated'[55] i.e., 'IBD is complicated'. In fact, both CD and UC are believed to be the result of the interaction of four major components, or -omes: the exposome (the external surrounding and internal body environment), the genome (the host's genetic makeup), the microbiome (the bacteria, fungi, viruses, and archaea harboured in the gut), and the immunome (the systemic and mucosal immune systems).

The exposome is exceedingly complex, changes continuously because of human intervention that makes it totally unpredictable, is impractical to qualify, and hard to quantify. The genome is structurally stable, individualised and qualifiable, but its function depends on gene–gene interactions and the exposome. The microbiome

is also extremely complex and individualised, varies continuously due to ingestion of food components, antibiotics, xenobiotics, and drugs; is hard to quantify and qualify; and is both exposome- and genome-dependent. The immunome is highly complex, constantly and variably adapting to immune and metabolic signals, is hard to quantify and only partially qualifiable, and is exposome-, genome- and microbiome-dependent. Each of these four factors comprises countless components and performs incalculable interactions, so that the resulting outcome (the IBD interactome) is variable, as it depends on the reciprocal and interdependent function of each -ome.[56] This leads to a more realistic definition IBD: IBD is a life-long, heterogeneous, and highly complex disease that cannot be cured by targeting one single disease component at any one time.

In addition, it should not be forgotten that humans are like snowflakes, 'no two are alike', and that the components of IBD are different and act differently in each patient with CD or UC. Each patient is exposed to and lives in a particular corner of the world, creating a distinct exposome, the genome is determined at the time of conception, and the gut microbiome results from a myriad of dietary and other factors that start right after birth and act for the rest of one's life. Consequently, when an IBD factor initiates the chain of events that will eventually result in IBD, each patient will use different receptors, activate different signalling molecules, bind different DNA loci, express and transcribe different genes, translate different proteins, and produce distinct pro-inflammatory products. These products may differ, but all will induce a damaging inflammatory process that will be recognised as IBD at the clinical level (Figure 1). So, if IBD is so complex, let's embrace its complexity to try to better understand it and look for different means to treat it.[57]

An initial consideration in IBD treatment is to ask the question: "What is being treated? Is the whole disease being treated, or simply the inflammation, which is the response to the disease?" About two decades ago, Carl Nathan wrote: "When primary pathogenetic events are unknown, control of inflammation is sometimes the next best option."[58] Since then, a lot of progress has been made in understanding pathogenic events in IBD, but healthcare professionals still adopt control of inflammation as the primary therapeutic approach for IBD. Indeed, when healthcare professionals consider the large variety of therapeutic options described above, it is obvious that current IBD therapies are utterly lopsided. There are no genetic therapies for IBD but, even if there were, they are unlikely to offer any significant benefit as genes alone do not cause IBD. Healthcare professionals can try to intervene in the exposome and change the patient's environment with lifestyle modifications such as diets and smoking cessation, which are predictably poorly accepted and hard to implement. Healthcare professionals can also modulate the microbiome via diets and administering antibiotics, probiotics, or faecal microbiota transplantation, but the results are incomplete and of short duration, as pointed out above. So, what is left is to target intestinal inflammation by the numerous and variable means mentioned above: 5-ASA compounds, corticosteroids, immunosuppressors, anti-cytokines, anti-chemokines, anti-receptors, anti-integrins, anti-signalling molecules, sphingosine-1-phosphate receptor agonists, leukapheresis, bone marrow transplants, and stem cell transplants. Combined, they represent roughly 90% of what can offer objective benefits to the patients, regardless of side effects and anticipated loss of efficacy (Figure 2).[59] As indicated above, the best response rates are still around 50% or less.[50] This unsatisfactory condition results directly from the single target-single medicine approach, and has remained unchanged for decades, indicating that a therapeutic ceiling has been reached, no matter what medication is prescribed.[40] Thus, it seems obvious that progress has stalled and innovative approaches to IBD therapy are needed.

HOW TO CHANGE THE THERAPEUTIC APPROACH TO INFLAMMATORY BOWEL DISEASE

If the complexity of IBD is accepted, and the fact that the single target-single medicine approach has stalled progress, one solution is to think about IBD in a completely different way. If IBD is complex, healthcare professionals should embrace its complexity: IBD has multiple components with multiple links,

comparable to what happens in most networks (social, financial, marketing, political, business, computer, etc.). Thinking in terms of an 'IBD network', a 'network medicine' approach should be applied. Network medicine is based on the principle that "rather than trying to force disease pathogenesis into a reductionist model, network medicine embraces the complexity of multiple influences on disease and relies on many different types of networks."[60] Intrinsic to the notion of network medicine is integration that, in the case of IBD, means to incorporate all pathogenic components into a unifying functional entity, the IBD interactome.[56] Interactomes are formed by innumerous biological components, but a series of technological tools are now available that can help to dissect complex biological systems, like transcriptomics, proteomics, epigenomics, single cell omics, and others, and all can be analysed and unified by computational modelling.[61] This approach generates what has come to be known as 'big data', i.e., a massive amount of information that can only be interpreted with the help of

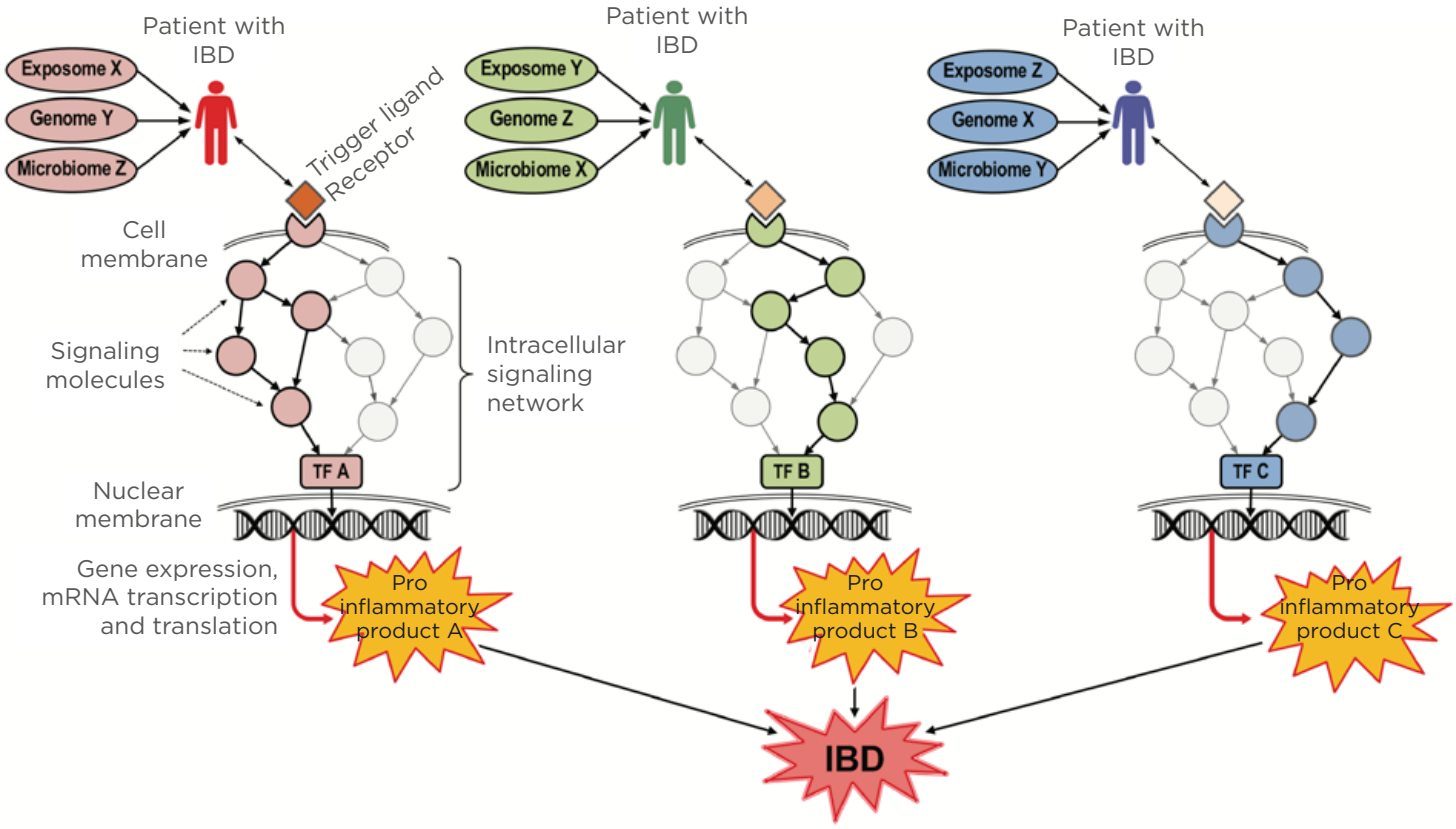

Figure 1: Schematic representation of how patients with inflammatory bowel disease use different pathogenic mechanisms that result in the same organotypic expression (intestinal inflammation).

All three patients (the red, green, and blue) were conditioned by the same key factors responsible for disease predisposition and expression, i.e., the exposome, the genome, and the microbiome. However, each of these conditioning factors differ in each patient (red patient: exposome X, genome Y, and microbiome Z; green patient: exposome Y, genome Z, and microbiome X; and blue patient: exposome Z, genome X, and microbiome Y). Consequently, when the disease is triggered by the binding of various ligands (drugs, chemicals, pollutants, toxins, food components, metabolites, hormones, microbes, etc.) to their cell receptors, distinct signalling and activation molecules are engaged in each patient, creating intracellular signalling networks that are unique to the red, green, and blue patients. As a result, each signalling network leads to the activation of distinct TFs (A, B, and C) that, once translocated into the nucleus, induce the expression of diverse inflammatory genes. Each gene is transcribed into mRNA and eventually translated into a particular pro-inflammatory product (A, B, and C) such as the cytokines TNF, IL-1, IL-6, IL-17, etc. that are secreted into the intestinal tissue microenvironment. Although each cytokine is unique, they all induce pro-inflammatory events, resulting in a largely non-specific form of inflammation with effects and manifestations that are clinically recognised as IBD.

IBD: inflammatory bowel disease; mRNA: messenger RNA; TF: transcription factor.

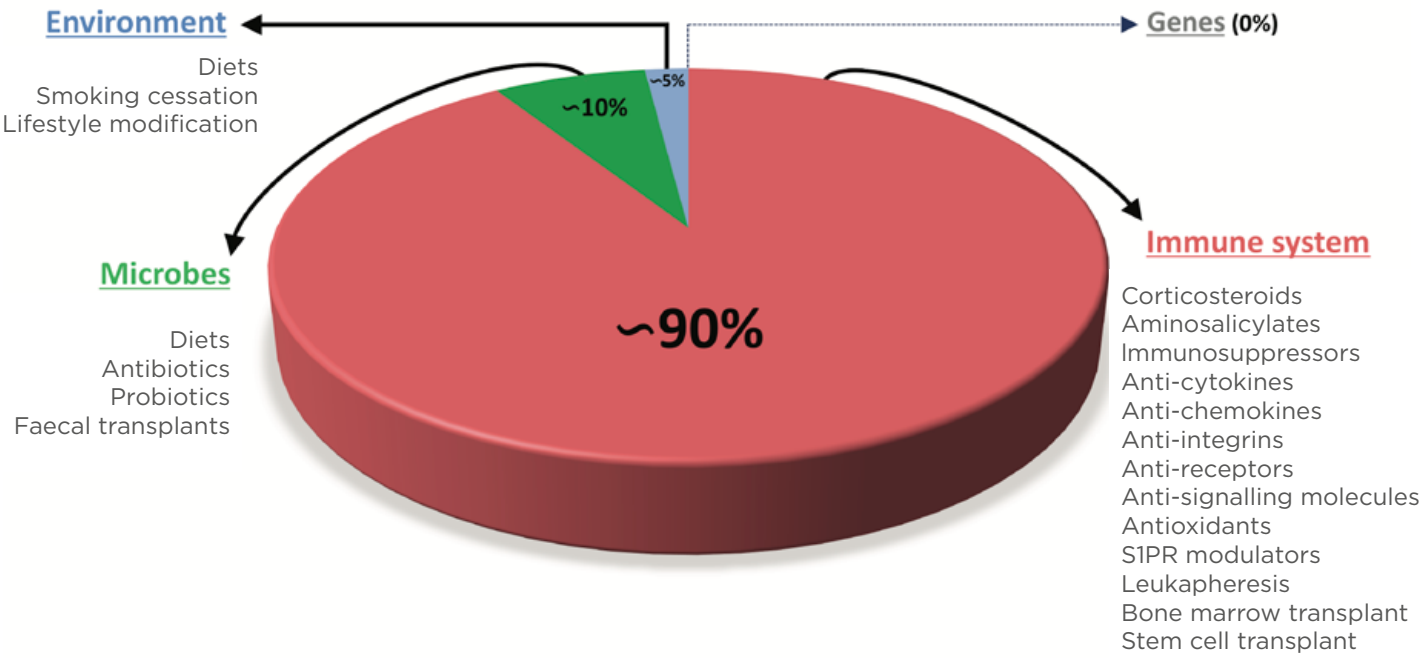

Figure 2: Relative proportion of the different therapeutic interventions available to treat inflammatory bowel disease by targeting the four major pathogenic factors.

There is no genetic therapy for CD or UC. Intervention on environmental factors can be attempted with diets, smoking cessation, and lifestyle modification but represents a tiny (approximately 5%) proportion of all treatment modalities. Modulation of the gut microbiota is approximately 10% of all possible therapeutic intervention. The immune system is the dominant (approximately 90%) form of treatment for IBD and can be accomplished with a large number of small molecules, biologics, and cell transplants.

CD: Crohn's disease; IBD: inflammatory bowel disease; S1PR: sphingosine-1-phosphate receptor; UC: ulcerative colitis.

machine learning and other types of artificial intelligence (AI).[62,63]

At this point, it is useful to establish an analogy between a network system and the IBD network (interactome). All networks have a 'hub', a dominant component that is usually centrally located and controls the function of all the peripheral components of the network. If the hub is disabled, the whole network is disrupted and ceases to function, being practically eliminated. Biological networks, including disease networks, function the same way, with central hubs and peripheral components,[64] and if the hub is disabled the disease is eliminated. Applying these concepts to the IBD network, there is a network composed of genes, environmental factors, microbes, immune cells, and other elements (Figure 3A). When healthcare professionals intervene at the periphery of the network, like currently done with antibiotics, immunosuppressants, and biologics, there have been some effect of variable degree, but the best effect is obtained when the disease hub is targeted (Figure 3B). If targeting of the disease hub is completely successful, then the whole disease network is disabled, and the disease is eliminated (Figure 3C).

To implement this strategy, the following steps are carried out: biosamples (blood, serum, tissues, stools, etc.) from patients with IBD and active and inactive disease as well as healthy controls are subjected to multi-omic analyses (genome, epigenome, transcriptome, microbiome, etc.); the respective molecular networks of each ome are identified; AI-based systems, such as machine-learning, integrate the different omic data; analysis of the integrated omic data generates the IBD network and identifies the hub of each network; the identified hub becomes the molecule to be therapeutically targeted; the biological relevance of the target to IBD is confirmed with biochemical, cellular, and animal studies; a computational docking platform to the crystal structure of the target is used to generate

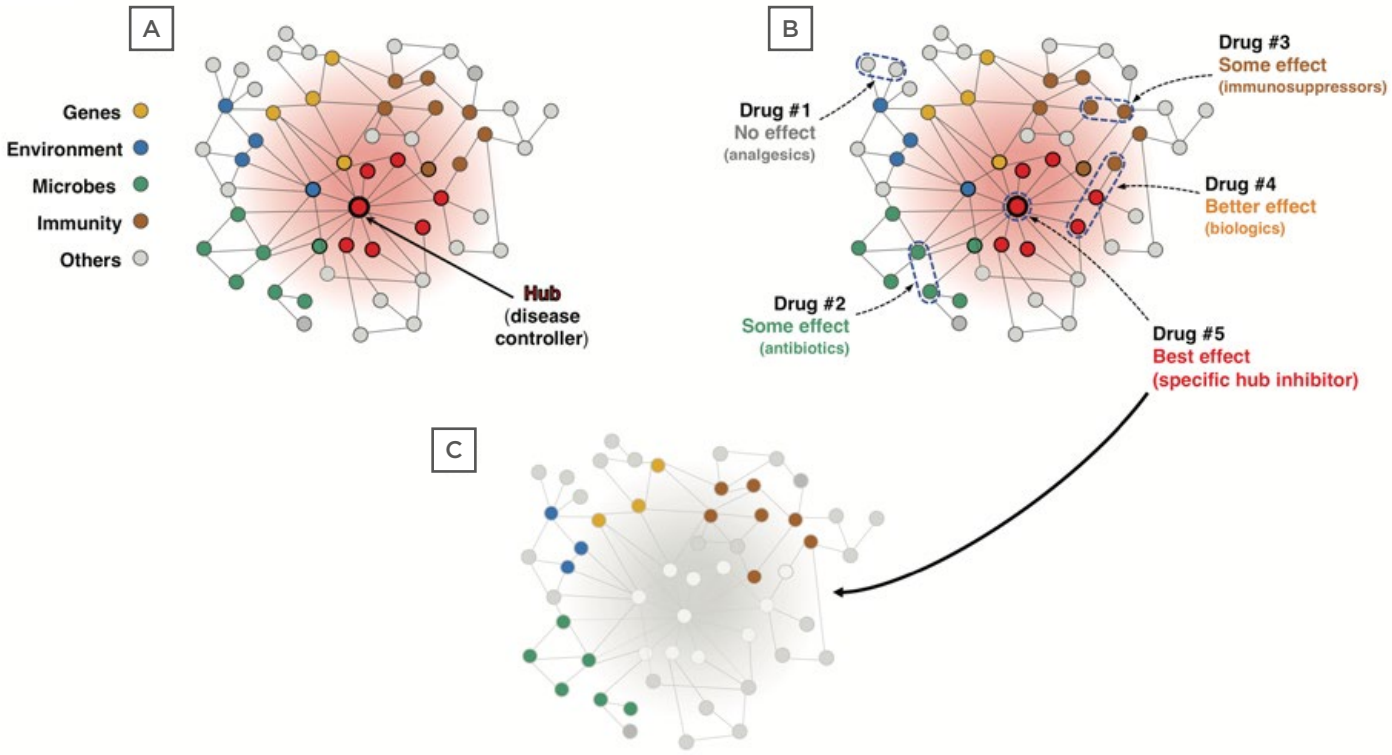

Figure 3: Graphical representation of the inflammatory bowel disease network and the effect of various therapeutic approaches.

A) The IBD network is composed of genes, environmental factors, microbes, immune cells, and other elements, and is controlled by a central hub, which can be a gene, a protein, a metabolite, a microbial product, a signalling molecule, an enzyme, etc. **B)** When a different way to try to disrupt the network is used, the results will vary depending on what part of the network is targeted. Drug #1 (analgesics) acts at the extreme periphery of the network and will have no effect; Drug #2 (antibiotics) acts on peripheral microbial components and may offer some benefit; Drug #3 (immunosuppressors) acts on immune components also peripherally located and will induce a partial response; Drug #4 (biologics) acts on some immune components plus other components more centrally located and will afford a better effect; and Drug #5 (specific hub inhibitor) will have the best effect by inhibiting the centrally located disease hub. **C)** Once the disease hub is disabled the whole disease network is disrupted and IBD is structurally and functionally eradicated.

IBD: inflammatory bowel disease.

small molecules inhibitors; the inhibitors are tested for drug–drug interactions, toxicity, and safety, and the overall best is clinically tested first in healthy volunteers and subsequently in patients. The newly identified drug will not be effective in all patients with IBD, but only those whose disease interactome is controlled by the specific hub against which the new drug was developed. With this strategy, different molecular subgroups of patients with IBD will be categorised, and each molecularly homogeneous subgroup will receive a specific drug that will target the hub controlling the disease in that subgroup.[65]

This omic- and AI-based approach will drastically change the way IBD is treated as each patient will receive drugs specifically designed for their underlying mechanism of disease, unlike drugs that broadly block mechanisms of inflammation. This approach fosters and speeds up the ongoing transition period between the old and the new. The old is the traditional physician-based approach based on classical medical tools (history, physical exam, blood chemistry, serology, stools exam, imaging, endoscopy, biopsy, and histology), that diagnoses and classifies patients with IBD based on traditional clinical phenotypes, and non-disease specific anti-inflammatory

drugs end up being prescribed. The new AI-based network approach to IBD therapy is not purely hypothetical but is actually under active development, with the discovery and targeting of newfound hubs in specific IBD subgroups and allowing the implementation of precision medicine.[66]

References

1. Alatab S et al. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol. 2020;5(1):17-30.
2. Baumgart D, Carding S. Inflammatory bowel disease: cause and immunobiology. Lancet. 2007;369(9573):1627-40.
3. Fiocchi C, Iliopoulos D. What's new in IBD therapy: An "omics network" approach. Pharmacol Res. 2020;159:104886.
4. Lichtenstein G et al. ACG clinical guideline: management of Crohn's disease in adults. Am J Gastroenterol. 2018;113(4):481-517.
5. Rubin D et al. ACG clinical guideline: ulcerative colitis in adults. Am J Gastroen-terol. 2019;114(3):384-413.
6. Blackwell J et al. Prevalence and duration of gastrointestinal symptoms before diagnosis of inflammatory bowel disease and predictors of timely specialist review: a population-based study. J Crohns Colitis. 2021;15(2):203-11.
7. Melmed G et al. Predicting a change in diagnosis from ulcerative colitis to Crohn's disease: a nested, case-control study. Clin Gastroenterol Hepatol. 2007;5(5):602-8.
8. Van Assche G et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. J Crohn Colitis. 2010;4(1):7-27.
9. Ferrante M et al. Outcome after proctocolectomy with ileal pouch-anal anastomosis for ulcerative colitis. Inflamm Bowel Dis. 2008;14(1):20-8.
10. Barnes E et al. The incidence and definition of Crohn's disease of the pouch: a systematic review and meta-analysis. Inflamm Bowel Dis. 2019;25(9):1474-80.
11. Langhol E. Current trends in inflammatory bowel disease: the natural history. Therap Adv Gastroenterol. 2010;3(2):77-86.
12. Present DH et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med. 1999;340(18):1398-405.
13. Svartz M. The treatment of 124 cases of ulcerative colitis with salazopyrine and attempts of desensibilization in cases of hypersensitiveness to sulfa. Acta Med Scand. 1948;131(Suppl 206):465-72.
14. Neurath MF. Current and emerging therapeutic targets for IBD. Nat Rev Gastroenterol Hepatol. 2017;14(5):269-78.
15. Ho GT et al. The efficacy of corticosteroid therapy in inflammatory bowel disease: analysis of a 5-year UK inception cohort. Aliment Pharmacol Ther. 2006;24(2):319-30.
16. Kuenzig M et al. Budesonide for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2014(8):CD002923.
17. Chande N et al. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Cochrane Database of Syst Rev. 2015(10):CD000067.
18. Feagan B et al. Methotrexate for the treatment of Crohn's Disease. The North American Crohn's Study Group. N Engl J Med. 1995;332(5):292-7.
19. Ledder O, Turner D. Antibiotics in IBD: Still a role in the biological era? Inflamm Bowel Dis. 2018;24(8):1676-88.
20. Townsend CM et al. Antibiotics for induction and maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2019;2(2):CD012730.
21. Naseer M et al. Prebiotics and probiotics in inflammatory bowel disease: where are we now and where are we going? Curr Clin Pharmacol. 2020;15(3):216-33.
22. Oliveira e Silva N et al. Probiotics in inflammatory bowel disease: does it work? World J Meta Anal. 2020;8(2):54-66.
23. Braegger CP et al. Tumour necrosis factor alpha in stool as a marker of intestinal inflammation. Lancet. 1992;339(8785):89-91.
24. Murch S et al. Location of tumour necrosis factor alpha by immunohistochemistry in chronic inflammatory bowel disease. Gut. 1993;34(12):1705-9.
25. Murch S et al. Serum concentrations of tumour necrosis factor alpha in childhood chronic inflammatory bowel disease. Gut. 1991;32(8):913-7.
26. Rutgeerts P et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353(23):2462-76.
27. Hanauer S et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial. Lancet. 2002;359(9317):1541-9.
28. Sandborn W et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut. 2007;56(9):1232-9.
29. Colombel JF et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology. 2007;132(1):52-65.
30. Colombel J-F et al. Four-year maintenance treatment with adalimumab in patients with moderately to severely active ulcerative colitis: data from ULTRA 1, 2, and 3. Am J Gastroenterol. 2014;109(11):1771-80.
31. Sandborn W et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146(1):96-109.
32. Schreiber S et al. Maintenance Therapy with certolizumab pegol for Crohn's disease. N Engl J Med. 2007;357(3):239-50.
33. Colombel JF et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010;362(15):1383-95.
34. Feagan BG et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369(8):711-21.
35. Sands B et al. Vedolizumab as induction and maintenance therapy for Crohn's disease in patients naïve to or who have failed tumor necrosis factor antagonist therapy. Inflamm Bowel Dis. 2017;23(1):97-106.
36. Feagan B et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2016;375(20):1946-60.
37. Sands B et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2019;381(13):1201-14.
38. Alsoud D et al. Breaking the therapeutic ceiling in drug development in ulcerative colitis. Lancet Gastroenterol Hepatol. 2021;6(7):589-95.
39. Ford A et al. Efficacy of biological therapies in inflammatory bowel

disease: Systematic review and meta-analysis. Am J Gastroenterol. 2011;106(4):644-59.

40. Ben-Horin S, Chowers Y. Review article: loss of response to anti-TNF treatments in Crohn's disease. Aliment Pharmacol Ther. 2011;33(9):987-95.
41. Sedki M et al. Natural history of colectomy among hospitalized patients with ulcerative colitis in the contemporary era of biologics. Inflamm Bowel Dis. 2020;26(Suppl 1):S44.
42. Munkholm P et al. Intestinal cancer risk and mortality in patients with Crohn's disease. Gastroenterology. 1993;105(6):1716-23.
43. Hanžel J, D'Haens GR. Anti-interleukin-23 agents for the treatment of ulcerative colitis. Expert Opin Biol Ther. 2020;20(4):399-406.
44. Sandborn W et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2017;376(18):1723-36.
45. D'Amico F et al. Tofacitinib in the treatment of ulcerative colitis: efficacy and safety from clinical trials to real-world experience. Therap Adv Gastroenterol. 2019;12:1756284819848631.
46. Fernández-Clotet A et al. JAK Inhibition: The most promising agents in the IBD pipeline? Curr Pharm Des. 2019;25(1):32-40.
47. Harris M et al. AVX-470, an orally delivered anti-tumour necrosis factor antibody for treatment of active ulcerative colitis: results of a first-in-human trial. J Crohns Colitis. 2016;10(6):631-40.
48. Misselwitz B et al. Emerging treatment options in inflammatory bowel disease: Janus kinases, stem cells, and more. Digestion. 2020;101(Suppl 1):69-82.
49. Wong C et al. Estimation of clinical trial success rates and related parameters. Biostatistics. 2019;20(2):273-86.
50. Alayo Q et al. Safety and effectiveness of combining biologics and small molecules in IBD: systematic review with meta-analysis. 2021. Available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3790447. Last accessed: 9 November 2021.
51. Stalgis C et al. Rational combination therapy to overcome the plateau of drug efficacy in inflammatory bowel disease. Gastroenterology. 2021;161(2):394-9.
52. Levine A et al. Evolving role of diet in the pathogenesis and treatment of inflammatory bowel diseases. Gut. 2018;67(9):1726-38.
53. Lightner AL. Stem cell therapy for inflammatory bowel disease. Clin Transl Gastroenterol. 2017;8(3):e82.
54. Levy A, Allegretti J. Insights into the role of fecal microbiota transplantation for the treatment of inflammatory bowel disease. Therap Adv Gastroenterol. 2019;12:1756284819836893.
55. Check Hayden E. Human genome at ten: life is complicated. Nature. 2010;464(7289):664-7.
56. de Souza HSP et al. The IBD interactome: an integrated view of aetiology, pathogenesis and therapy. Nat Rev Gastroenterol Hepatol. 2017;14(12):739-49.
57. Embrace the complexity. Nature Immunol. 2009;10(4):325.
58. Nathan C. Points of control in inflammation. Nature. 2002;420(6917):846-52.
59. Hernandez-Rocha C, Vande Casteele N. JAK inhibitors: current position in treatment strategies for use in inflammatory bowel disease. Curr Opin Pharmacol. 2020;55:99-109.
60. Loscalzo J et al. (eds.), Network Medicine: Complex Systems in Human Disease and Therapeutics (2017) Harvard University Press: Cambridge, Massachusetts, p.448.
61. Yosef N, Regev A. Writ large: genomic dissection of the effect of cellular environ-ment on immune response. Science. 2016;354(6308):64-8.
62. Rajkomar A et al. Machine learning in medicine. N Engl J Med. 2019;380(14):1347-58.
63. le Berre C et al. Application of artificial intelligence to gastroenterology and hepatology. Gastroenterology. 2020;158(1):76-94.
64. Barabási AL et al. Network medicine: a network-based approach to human disease. Nat Rev Genet. 2011;12(1):56-68.
65. Fiocchi C et al. Results of the Seventh Scientific Workshop of ECCO: precision medicine in IBD - what, why, and how. J Crohn Colitis. 2021;15(9):1410-30.
66. Yadav A et al. Precision medicine - networks to the rescue. Cur Opin Bio-technol. 2020;63:177-89.

Fertility and Pregnancy Outcomes after High-Intensity Focused Ultrasound Ablation for Uterine Fibroids and Adenomyosis: A Review

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Abstract

High-intensity focused ultrasound (HIFU) ablation, also known as focused ultrasound surgery, is the latest advancement in treating uterine fibroids and adenomyosis. Limited evidence, in terms of case series only, suggest that ultrasound-guided focused ultrasound/magnetic resonance-guided focused ultrasound treatment for fibroids and adenomyosis could be a safe alternative to myomectomy or uterine artery embolisation for females who wish to have babies. It also appears that this non-invasive HIFU treatment can shorten the treatment to pregnancy interval after HIFU ablation. Further studies are needed to confirm such findings.

INTRODUCTION

Uterine fibroids and adenomyosis are common among reproductive-age females. Uterine fibroids, particularly large submucosal and intramural uterine fibroids, may cause infertility and implantation and miscarriage problems.[1,2] They may also increase the risk of complications during pregnancy and delivery; during pregnancy, they may cause inappropriate enlargement of the uterus, fetal malpresentation, obstructed labour, caesarean delivery, and post-partum haemorrhage.[3,4]

Adenomyosis, though arising from different aetiology, may also cause similar problems. Furthermore, adenomyosis can interfere with the process of pregnancy by disrupting implantation.[5] They are also the most common cause for heavy menstrual bleeding, leading to anaemia before contemplating pregnancy.[6] Medical treatments with hormones or progestogen intrauterine contraceptive devices prevent these patients from conception and pregnancy. Therefore, surgical treatment is the usual resort to improve their chance of pregnancy.[7]

METHODOLOGY

Methodology of this study of high-intensity focused ultrasound (HIFU) ablation involved literature search using PubMed as the search engine and using keywords such as 'high-intensity focused ultrasound', 'HIFU', 'fibroid',

'adenomyosis', and 'pregnancy' from 2001 to 2021. Additional literature searches were conducted from peer-reviewed colleges' publications and guidelines, as well as of references from the co-author's books: *Adenomyosis Facts and Treatments* by Xue et al.[8] and *Focused Ultrasound Surgery in Gynecology* by Wong et al.[9]

WHAT IS HIGH-INTENSITY FOCUSED ULTRASOUND AND HOW IT WILL HELP TO IMPROVE FERTILITY?

HIFU ablation, also known as focused ultrasound surgery (FUS), is the latest advancement in treating many benign solid tumours in gynaecology and surgical conditions,[10-14] including, but not limited to, uterine fibroids and adenomyosis.[12,15-17] It is non-invasive, in which the most striking feature is no cut wound of the uterine wall in which the lesions are located.

HIFU focuses the ultrasound energy on the target lesions such as uterine fibroids or adenomyosis without affecting the surrounding organs. The localised temperature to the target lesion is 60–90 °C. The surrounding tissue and vessels under lower temperature dissipate the heat by their blood flow. Therefore, the damage to the surrounding tissue and vessels could be minimised when the HIFU heat is applied in a pulsed manner. This induces coagulation necrosis of the uterine fibroids or adenomyosis without damage to the surrounding organs, particularly the major vessels. Subsequently, the necrotic fibroid or adenomyosis tissues are absorbed and removed, leading to reduced sizes of the treated lesions.

After HIFU treatment, either with the use of ultrasound or MRI to assess the size of fibroids, most of the fibroids reduce at least 50.0% in size after a single treatment. Lyon et al.[18] reported a case series of 10 patients, with a 23.3% reduction in size at 3 months, 49.3% at 12 months, and 51.9% at 24 months. A retrospective case series of 189 nulliparous females also showed the mean reduction in uterine fibroids volume was 58.0%±31.3% in 12 months after HIFU ablation.[19] These reductions in uterine sizes greatly enhance the fertility environment of the uterus for pregnancy. HIFU also has a strong advantage in maintaining the integrity of the uterus. Using ultrasound focusing on ablating adenomyosis lesions can restore the uterus's anatomy and improve the immune microenvironment; the pregnancy rate increased after HIFU treatment for adenomyosis.[20]

HIGH-INTENSITY FOCUSED ULTRASOUND TECHNIQUE

The target adenomyosis tissue is identified through visualisation by comparing ultrasound and MRI images during HIFU treatment. HIFU ablation is performed to ablate the adenomyosis tissue point by point, layer by layer, until grey-scale changes of the coagulated tissue are obvious. Under MRI, it is not too difficult after to identify the irregular boundary between adenomyosis and normal myometrium. Improving static ultrasound technology helps to identify adenomyosis; also, using cine clips (movie editing function) if available can easily diagnose adenomyosis.[8]

HIGH-INTENSITY FOCUSED ULTRASOUND ABLATION COMPARED WITH MYOMECTOMY OR ADENOMYOMECTOMY

Myomectomy or adenomyomectomy are also performed on patients who wish to retain their uterus, but fibroid recurrence rates after abdominal myomectomy are 12.4% and 46.0% at 12 and 24 months, respectively.[21] The need for re-operation for recurrent symptoms in adenomyosis is high. The risk of recurrence of uterine fibroid after HIFU is 15%, which is lower or at least comparable with myomectomy. These surgical procedures are also associated with morbidity or even mortality.

HIFU ablation is a new technology. Its safety profile is best-known in treating space-occupying lesions in gynaecology. Furthermore, the reported complications are minor. Chen et al.[22] demonstrated in a large cohort study that complications arising from HIFU ablation were all Grade A or B but not C or above, according to the Society of Interventional Radiology (SIR) Severity Classification standard.[23] In another safety analysis of 9,988 cases of uterine fibroids and adenomyosis treated by HIFU ablation, Chen et al.[24] noted that more serious complications occurred when treating

adenomyoma, reflecting the difference in the pathology of the two different types of disease. However, the incidence of complications in HIFU ablation is comparatively low.[25]

After HIFU ablation, improvement of symptoms and quality of life were significantly better than surgical myomectomy.[26] The improvement of haemoglobin level enhances successful pregnancy and delivery outcomes.

After myomectomy, patients who may become pregnant have risks of uterine rupture, miscarriage, pre-term birth, and intrauterine adhesions that impair pregnancy.[27] These patients are also advised not to get pregnant within 1–2 years to allow the uterine wound to heal well before pregnancy. Even if previous surgery had not affected the chance of pregnancy, the mode of delivery is still controversial. When myomectomy, or uncommonly adenomyomectomy, has been performed on a female with fibroids or adenomyosis, some obstetricians may allow a trial of a vaginal birth if there is no endometrial opening of the uterine cavity during myomectomy. However, some doctors in some Asian countries, because of the unavailable detailed history of previous myomectomy or adenomyomectomy, may choose to offer elective caesarean section to avoid risk of uterine rupture during labour.

COMPARISON WITH UTERINE ARTERY EMBOLISATION

HIFU ablation is a non-invasive procedure that has often been compared with uterine artery embolisation (UAE), which has also been accepted as an effective alternative treatment for uterine fibroids and adenomyosis instead of surgery.[28,29] However, regarding fertility, pregnancy, and delivery outcomes, major complications include uterine necrosis and infection leading to emergent hysterectomy, ovarian failure, amenorrhoea, and vaginal dryness related to non-target embolisation or over-embolisation.[30,31] At present, there is no definite conclusion about the safety of pregnancy after UAE. There are reports of cases of successful pregnancy and delivery after UAE; however, adverse outcomes of pregnancy after UAE including spontaneous abortion, premature delivery, abnormal placenta, pre-eclampsia, post-partum haemorrhage, etc., have also been observed,[32,33] and the rate of caesarean section has also increased. Therefore, for females considering future pregnancy, UAE should be carefully considered for its impact after treating fibroids or adenomyosis.[28]

COMPARISION WITH MEDICAL TREATMENT

There is no long-lasting, effective medical treatment to reduce the size of uterine fibroids, including short interval treatment with ulipristal. Hence it is not advisable to use medical treatment alone in the management of pressure symptoms secondary to uterine fibroids.

On the other hand, there are many existing reports showing that after HIFU ablation treatment for fibroids and adenomyosis there was no adverse impact on fertility, pregnancy, and labour outcomes.

Impact on Fertility

There has been concern that HIFU ablation might affect the ovarian function or fertility reserve. Lee et al.[34] compared the anti-Müllerian hormone (AMH) levels of 70 patients with symptomatic adenomyosis and uterine fibroids before and 6 months after HIFU ablation. They found no significant difference in AMH levels between the two treatment groups, suggesting that HIFU ablation has minimal impact on ovarian reserve. No AMH changes after HIFU ablation was also confirmed by Cheung et al.[35] in their study. Therefore, it appears that HIFU ablation is comparatively safer for the fertility of patients receiving treatment.

So far, there has not been a study that demonstrates the impact of HIFU sonication, particularly for a submucosal fibroid and its adjacent endometrial tissue, causing any impairment of implantation. As a result of indirect sonication, the ultrasound energy may impair uterine functions. Direct and excessive ablation of a submucous fibroid might also cause intracavitary adhesions or denuded endometrial lining. Nevertheless, despite a lack of case reports, this possibility cannot be excluded.

Impact on Pregnancy

In the early days of magnetic resonance-guided (MRg)-HIFU treatment, case reports of pregnancies showed successful vaginal delivery at term, and none had complications during pregnancy and labour.[36,37] Some larger studies, including individual and multicentre collaborative trials, have also confirmed successful pregnancies after HIFU ablation for fibroids and adenomyosis.[38-41]

As many studies were from China, the authors had reported a high rate of induced abortions and miscarriage in pregnancies after HIFU treatment for fibroids and adenomyosis. However, it might be related to the fertility regulation in the past. It is also possible that maternal age and sizable fibroids after HIFU may also influence the miscarriage rate in any study, as both factors can independently adversely impact miscarriages. Bohlmann et al.[42] showed that the risk of miscarriage after ultrasound-guided (USg)FUS/MRgFUS was 17.8%, which did not appear to be higher than a control group of patients wanting to have children.

Impact on Delivery

From the literature, normal pregnancies have been reported 3–5 months after HIFU treatment.[43,44] These patients had uneventful vaginal deliveries. There was no uterine rupture during pregnancy or labour for those with vaginal delivery at term after HIFU treatment. Therefore, it appears from these limited data that pregnancy can occur within 1 year after HIFU treatment and a good pregnancy outcome is possible. Conception is advisable 6 months after HIFU.

HIFU delivers pulsed HIFU to the target lesion of uterine fibroid, whereas myomectomy aims to remove the target uterine fibroid. After myomectomy, caesarean section is needed if the uterine cavity has been entered during surgery.

Despite the widespread reassurance that vaginal delivery is safe, the rate of elective caesarean section appeared to be high among females after HIFU ablation. The caesarean section rate was reported as high as 50–78%.[38,44] After HIFU ablation, all pregnancies that reach term would have a high caesarean section rate compared to term pregnancy without HIFU surgery. The reasons for the high caesarean section rate are not known; this might be due to a maternal preference.

CONCLUSION

There is currently no systematic study on the effects on fertility, pregnancy, and delivery outcome for patients after HIFU ablation treatment for fibroids and adenomyosis, but there have been a large number of cases of pregnancy and related reports, suggesting that there is little effect after HIFU on pregnancy. The number of patients requiring continued childbirth is still small, and there is not enough scientific evidence to explain the impact on mother and child during pregnancy.

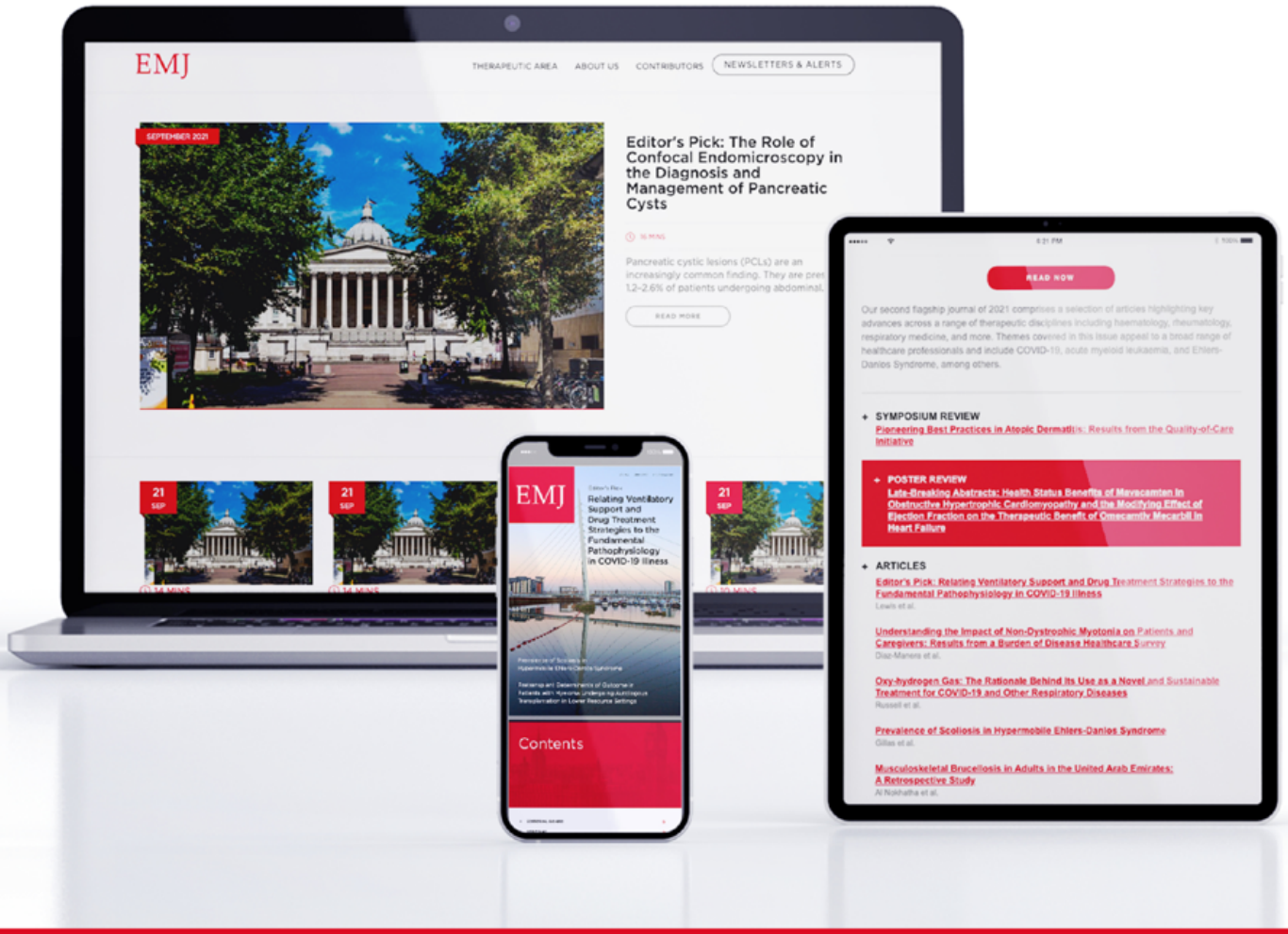
The current consensus among HIFU doctors, but with limited evidence, suggests that USgFUS/MRgFUS treatment for fibroids and adenomyosis could be a safe alternative to myomectomy or UAE for females who wish to have babies. It also appears that this non-invasive HIFU treatment can shorten the treatment to pregnancy interval after HIFU ablation. Given the prevalence of females with fibroids and adenomyosis before childbearing, addressing these important reproductive issues in a large clinical trial is critical.

References

1. Mirzamoradi M et al. Evaluation of pregnancy outcomes in Iranian women with uterine myomas. Novelty in Biomedicine. 2020;8(3):142-5.
2. Serour AG. Adenomyosis a forgotten cause of infertility. The Egyptian Journal of Fertility of Sterility. 2020;24(2):11-21.
3. Lee HJ et al. Contemporary management of fibroids in pregnancy. Rev Obstet Gynecol. 2010;3(1):20-7.
4. Mehla S, Singh N. Assessment of pregnancy outcome in patients with uterine fibroids. JAMDSR. 2020;8(11):145-8.
5. Harada T et al. The impact of adenomyosis on women's fertility. Obstet Gynecol Surv. 2016;71(9):557-68.
6. Halvorson LM. New perspectives on adenomyosis. Semin Reprod Med. 2020;38(2-03):87-8.
7. Szubert M et al. Adenomyosis and Infertility—review of medical and

surgical approaches. Int J Environ Res Public Health. 2021;18(3):1235.

8. Xue M et al., Ultrasound scanning Skill for Adenomyosis: Adenomyosis Facts and treatments (2021) 1st edition, Singapore: Springer, p.70.
9. Wong F et al. (eds.), Focused Ultrasound Surgery in Gynecology (2021) 1st edition, Singapore: Springer.
10. Maloney E, Hwang JH. Emerging HIFU applications in cancer therapy. Int J Hyperthermia. 2015;31(3):302-9.
11. Huang L et al. High-intensity focused ultrasound combined with dilatation and curettage for caesarean scar pregnancy. Ultrasound Obstet Gynecol. 2014;43(1):98-101.
12. Yang T et al. HIFU for the treatment of difficult colorectal liver metastases with unsuitable indications for resection and radiofrequency ablation: a phase I clinical trial. Surgical Endosc. 2020;35(5):1-10.
13. Marinova M et al. Improving quality of life in pancreatic cancer patients following high-intensity focused ultrasound (HIFU) in two European centers. Eur Radiol. 2021;31(8):1-12.
14. Ziglioli F et al. Oncologic outcome, side effects and comorbidity of high-intensity focused ultrasound (HIFU) for localised prostate cancer. A review. Ann Med Surg (Lond). 2020;56:110-5.
15. Shui L et al. High-intensity focused ultrasound (HIFU) for adenomyosis: two-year follow-up results. Ultrason Sonochem. 2015;27:677-81.
16. Marinova M et al. Novel non-invasive treatment with high-intensity focused ultrasound (HIFU). Ultraschall Med. 2016;37(1):46-55.
17. Li X et al. High-intensity focused ultrasound in the management of adenomyosis: long-term results from a single center. Int J Hyperthermia. 2021;38(1):241-7.
18. Lyon P et al. Ultrasound-guided high intensity focused ultrasound ablation for symptomatic uterine fibroids: preliminary clinical experience. Ultraschall Med. 2020;41(5):550-6.
19. Shu Li J et al. Pregnancy outcomes in nulliparous women after ultrasound ablation of uterine fibroids: a single-central retrospective study. Sci Rep. 2017;7(1):3977.
20. Huang YF et al. A comparison of reproductive outcomes of patients with adenomyosis and infertility treated with high-intensity focused ultrasound and laparoscopic excision. Int J Hyperthermia. 2020;37(1):301-7.
21. Nishiyama S et al. High recurrence rate of uterine fibroids on transvaginal ultrasound after abdominal myomectomy in Japanese women. Gynecol Obstet Invest. 2006;61(3):155-9.
22. Chen J et al.; Committee of the ClinicalTrial of HIFU versus Surgical Treatment for Fibroids. Evaluation of high-intensity focused ultrasound ablation for uterine fibroids: an IDEAL prospective exploration study. BJOG. 2018;125(3):354-64.
23. Khalilzadeh O et al. Proposal of a new adverse event classification by the society of interventional radiology standards of practice committee. J Vasc Interv Radiol. 2017;28(10):1432-7.
24. Chen J et al. Safety of ultrasound-guided ultrasound ablation for uterine fibroids and adenomyosis: a review of 9988 cases. Ultrason Sonochem. 2015;27:671-6.
25. Felix Wong WS et al. Adenomyosis - is a new treatment solution available? Clin Exp Obstet Gynecol. 2021;48(1):5-8.
26. Wang F et al. Ultrasound-guided high-intensity focused ultrasound vs laparoscopic myomectomy for symptomatic uterine myomas. J Minim Invasive Gynecol. 2014;21(2):279-84.
27. The Hong Kong College of Obstetricians and Gynaecologists (HKCOG). Guidelines for the management of uterine leiomyoma. 2009. Available at: https://www.hkcog.org.hk/hkcog/Download/Guidelines_for_the_Management_of_Uterine_Leiomyoma_2009.pdf. Last accessed: 8 November 2021.
28. de Bruijn AM et al. Uterine artery embolisation for the treatment of adenomyosis: a systematic review and meta-analysis. J Vasc Interv Radiol. 2017;28(12):1629-42.
29. Spies, J.B., et al., Uterine artery embolisation for leiomyomata. Obstet Gynecol. 2001. 98(1):29-34.
30. Spies JB et al. Complications after uterine artery embolization for leiomyomas. Obstet Gynecol. 2002;100(5):873-80.
31. Toor SS et al. Complication rates and effectiveness of uterine artery embolisation in the treatment of symptomatic leiomyomas: a systematic review and meta-analysis. AJR Am J Roentgenology. 2012;199(5):1153-63.
32. Spies JB et al. Ovarian function after uterine artery embolisation for leiomyomata: assessment with use of serum follicle stimulating hormone assay. J Vasc Interv Radiol. 2001;12(4):437-42.
33. Pron G et al. Pregnancy after uterine artery embolisation for leiomyomata: the Ontario multicenter trial. Obstet Gynecol. 2005;105(1):67-76.
34. Lee JS et al. Ultrasound-guided high-intensity focused ultrasound treatment for uterine fibroid & adenomyosis: a single center experience from the Republic of Korea. Ultrason Sonochem. 2015;27:682-7.
35. Cheung VY et al. Ovarian reserve after ultrasound-guided high-intensity focused ultrasound for uterine fibroids: preliminary experience. J Obstet Gynaecol Can. 2016;38(4):357-61.
36. Hanstede MM et al. Focused ultrasound surgery of intramural leiomyomas may facilitate fertility: a case report. Fertil Steril. 2007;88(2):497
37. Morita Y et al. Pregnancy following MR-guided focused ultrasound surgery for a uterine fibroid. Int J Gynecol Obstet. 2007;99(1):56-7.
38. Rabinovici J et al. Pregnancy outcome after magnetic resonance–guided focused ultrasound surgery (MRgFUS) for conservative treatment of uterine fibroids. Fertil Steril. 2010.93(1):199-209.
39. Zou M et al. Pregnancy outcomes in patients with uterine fibroids treated with ultrasound-guided high-intensity focused ultrasound. BJOG. 2017;124(3):30-5.
40. Liu X et al. Vaginal delivery outcomes of pregnancies following ultrasound-guided high-intensity focused ultrasound ablation treatment for uterine fibroids. Int J Hyperthermia. 2018;35(1):510-7.
41. Wang Z et al. Observation on pregnancy outcomes after high intensity focused ultrasound ablation therapy in patients with adenomyosis. Chongqing Medicine. 2017;36:2506-8.
42. Bohlmann MK et al. High-intensity focused ultrasound ablation of uterine fibroids–potential impact on fertility and pregnancy outcome. Geburtshilfe Frauenheilkunde. 2014;74(02):139-45.
43. Kim KA et al. Short-term results of magnetic resonance imaging-guided focused ultrasound surgery for patients with adenomyosis: symptomatic relief and pain reduction. Fertil Steril. 2011.95(3):1152-5.
44. Rabinovici J et al. Pregnancy and live birth after focused ultrasound surgery for symptomatic focal adenomyosis: a case report. Hum Reprod. 2006.21(5):1255-9.
45. Shu Li J et al. Pregnancy outcomes in nulliparous women after ultrasound ablation of uterine fibroids: a single-central retrospective study. Sci Rep. 2017;7(1):3977.



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Ovarian Transposition Strategy in Patients with Cervical Cancer Who Undergo Pelvic Radiation: Proposal of Ovarian Placement Based on Virtual Simulations

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Abstract

Objective: To establish a proposal for the location for ovarian transposition, considering different irradiation techniques and time to ovarian failure.

Methods: Patients with cervical cancer in childbearing age submitted to adjuvant radiotherapy were selected. Delineation of simulated positions of the ovaries and pelvic radiation planning was done in CT, with three techniques: 3D conformal radiotherapy, intensity-modulated radiotherapy, and volumetric modulated arc radiotherapy. In order to correlate the ovaries maximal doses with the time to ovarian failure, the authors have used the one adaptation of Wallace model that predicts oocytes survival rates after radiation exposure.

Results: Thirteen patients who were being treated between 2008 and 2017 were studied. When the ovaries were positioned 10 cm cranially from the sacral promontory, the pelvic radiation entails a decrease of 20% in the time to ovarian failure compared with that expected for a female at the same age without irradiation exposition. The placement of the ovaries <5 cm cranially from the sacral promontory results in a decrease >90%. There was no difference in time to ovarian failure between the radiation treatment techniques tested: 3D conformal radiotherapy, intensity-modulated radiotherapy, and volumetric modulated arc radiotherapy (p=0.197).

Conclusions: The present study, based on virtual simulations, is the first to use the sacral promontory as a reference for a proposal of ovarian location with transposition. The authors have correlated the position of the ovaries and percentage of decrease in time to ovarian failure. These findings can potentially improve the management and counselling of patients with cervical cancer in childbearing age and deserve clinical validation.

INTRODUCTION

Cervical cancer is a public health problem worldwide, with an annual incidence of 528,000 new cases and 226,000 deaths.[1] The distribution of the disease is bimodal, with a peak at 35–39 years old and a second peak at 75–79 years old.[2] It is estimated that >30% of cervical cancers are diagnosed in females in their reproductive age.[3] Treatment of cervical cancer is based on surgery, radiotherapy, and chemotherapy. The best therapeutic choice must consider the disease's staging, age, clinical condition, available local resources, and the patient's desire for family planning and preservation of fertility.

Despite playing a key role in the management of cervical cancer, radiation can induce premature ovarian failure. Radiotherapy is now a well-known cause of ovarian damage, leading earlier menopause with permanent infertility. Doses >6 Gy in total body irradiation in young people induce premature ovarian failure, whereas prepubertal individuals can tolerate even higher radiation doses.[4] Wallace et al. demonstrated that the dose necessary to destroy 50% of the primordial follicles is less than 2 Gy[5] and that 4 Gy can produce infertility in one-third of young females and in almost all females over the age of 40 years.[6] The degree of ovarian impairment is related to the volume treated, total irradiation dose, fractionation schedule, and age at the time of treatment, with older people being at greater risk of damage.[7]

In addition to issues related to the reproductive future arising from the ovarian failure, premature menopause is associated with cardiovascular disease, osteoporosis, genital atrophy, vasomotor symptoms, and a significant impact on quality of life.[8] The term 'induced menopause' has been defined by the North American Menopause Society (NAMS) as the cessation of menstruation following bilateral oophorectomy or iatrogenic ablation of ovarian function resulting from delivery of chemotherapy or pelvic radiation.[9] The onset of symptoms can occur within 12 weeks of initiation of pelvic radiation therapy.[10] Management of climacteric symptoms is critical in efforts to optimise the quality of life. However, potential hormone stimulation has raised concern over the safety of hormone therapy in this population.[11-13]

In order to minimise the effects of induced menopause, ovarian transposition or oophoropexy can be surgically performed to remove the ovaries from the area to be irradiated. This procedure may prevent induced menopause and ovaries may be used at a later date for oocyte retrieval, *in vitro* fertilisation, and achieving pregnancy through surrogacy if appropriate.[14] Ovarian transposition is also described in the context of paediatric tumours and some pelvic neoplasms in young women for the purpose of ovarian and even fertility preservation.[15,16] This procedure can be performed by laparotomy or laparoscopy, it has low morbidity, is safe from the oncological point of view, and, in the context of patients with cervical cancer, may be indicated for young patients with indication of radiation.[17-20]

Techniques have been described to relocate the ovaries to the paracolic gutters, behind the uterus, or to anterolateral positions above the umbilicus.[21] There is no consensus as to where is the best position in which the ovaries should be implanted.[16,22-26] Therefore, the aim of this study was to establish a proposal, based on virtual simulations, to suggest the location of the ovaries in the transposition, considering different radiation techniques and time to ovarian failure.

MATERIALS AND METHODS

The patients evaluated included females diagnosed with cervical cancer in childbearing age, defined as age under 51 years, without climacteric symptoms, submitted to adjuvant pelvic radiotherapy, where all treatments did not use any type of ovarian preservation such as ovarian transposition. Electronic medical records were used to collect their pathological staging, histological type, patient's age, weight, height, and BMI at time of diagnosis. The present study was approved by the ethics committee of the involved institution. According to the criteria above, the authors retrospectively identified 13 patients treated between January 2008 and July 2017.

The CT obtained was used for the virtual simulation of the transposed ovaries and for radiotherapy planning. Delineation of the positions of 54 of the simulated ovaries was performed by two radiation oncologists and two experienced oncology gynaecologists. Radiotherapy planning was performed in three

different techniques: 3D conformal radiotherapy, intensity-modulated radiation therapy (IMRT), and volumetric modulated arc therapy (VMAT), all using beams of 10 MV with dose prescription of 45 Gy with 95% of coverage in target volume. The target volume used for radiotherapy planning was planning target volume, which consisted of the clinical target volume (CTV) plus a 5 mm margin. The CTV contouring included the common, external, internal iliac, and presacral lymph node region. The upper 3 cm of the vagina and paravaginal soft tissue lateral to the vagina were also included. The superior border of the CTV began 5–7 mm below the L4–L5 interspace, such as would customarily be used in a conventional four-field box.[27]

Intending to associate the dose received by the ovaries with its function, the survival equation obtained by Wallace et al.[28] was used. The theoretical decrease in time to ovarian failure in percentage was calculated as a ratio between the time to ovarian failure after a specified radiation dose and time to ovarian failure with no radiation exposure. The algorithm was applied for the maximum dose values in each outlined structure that simulated the ovarian position. The distance between the sacral promontory and the inferior border of the simulated ovaries in the cranial–caudal axis was associated with time to ovarian failure. The authors also evaluated the impact of mediolateral and anteroposterior displacement in time to ovarian failure.

STATISTICAL ANALYSIS

For the statistical analysis, R software (version 3.4.2) was used. The effect of the distance between the sacral promontory and the inferior border of the simulated ovaries in the cranial–caudal axis on premature ovarian failure was studied with three non-linear regression models: Log-Logistic, Weibull, and Log-Normal. In order to select the best model, the Akaike information criterion was used.[29,30] According to this method, the Weibull model was selected. To verify if the relationship between the decrease in time to ovarian failure and distance from sacral promontory and the inferior border of the simulated ovaries in the cranial–caudal axis was different between the radiation techniques, heights, weights, and BMIs, analysis of variance, often referred to as ANOVA, was used.[31] Then, models were adjusted for each of the classes of interest that were obtained through the median of the variables. In all models, the fit quality was verified by the 'lack-of-fit' test.[32]

RESULTS

The majority of the patients had squamous cell carcinoma, Stage IB or IIA. Regarding the characterisation variables, these are presented as mean±standard deviation. The mean age of the patients was 36.4±8.6 years, the mean height was 1.61±0.05 m, the mean weight was 69±20 kg, and the mean BMI was 26.8±8.3 kg/m^2, with the minimum of 20.8 kg/m^2 and the maximum of 46.7 kg/m^2.

Different positions of the simulated ovaries in the mediolateral and anteroposterior axis did not show any difference in time to ovarian failure. Figure 1 shows the relationship between the decrease in time to ovarian failure and distance from sacral promontory to the inferior border of the simulated ovaries in the cranial–caudal axis. It is possible to verify that ovaries positioned 10 cm cranially from the sacral promontory result in a decrease of 20% in the time to ovarian failure compared with what would be expected for a woman at the same age without radiation exposure. The placement of the ovaries <5 cm cranially from the sacral promontory resulted in a decrease >90% in the time to ovarian failure. There was no difference in ovarian preservation between the 3D conformal radiotherapy, IMRT, and VMAT techniques (p=0.197).

Table 1 illustrates the decrease in the time to ovarian failure after specified radiation dose received by the ovaries compared with non-irradiated females of the same age associated to the different positions of the ovaries cranially from the sacral promontory. According to the 'lack-of-fit' test, the model presented a good fit (p=1.000). For simulated ovaries positioned 7 cm above the promontory in the caudal–cranial axis, the mean dose was 6.7 Gy or smaller and the decrease in time to ovarian failure would be <50%, whereas for ovaries positioned 10 cm above the promontory the mean dose would be 1.4 Gy or smaller and the decrease in time to ovarian failure would be <20% (Figure 2). These findings were consistent regardless of the patient's height, weight, and BMI.

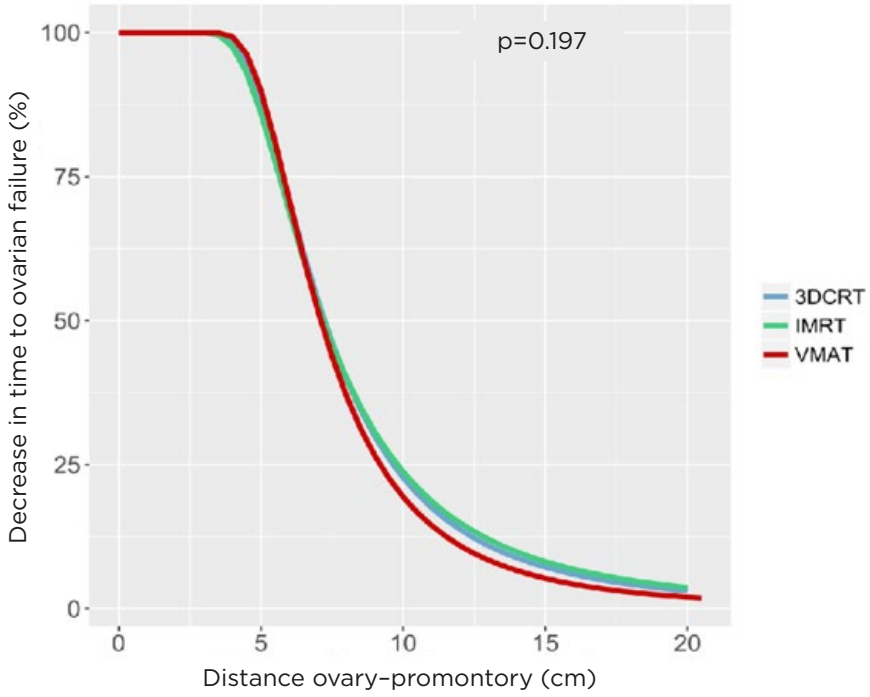


Figure 1: The relationship between the decrease in time to ovarian failure and the distance from sacral promontory in cranio–caudal axis to inferior border of the ovaries.

IMRT: intensity-modulated radiotherapy; VMAT: volumetric modulated arc radiotherapy; 3DCRT: 3D conformal radiotherapy.

Table 1: Decrease in the time to ovarian failure compared with non-irradiated females associated to the different positions of the ovaries cranially from the sacral promontory.

Decrease in the time to ovarian failure (%)	Cranial distance from the sacral promontory (95% CI) (cm)
90	4.9 (4.7–5.0)
80	5.5 (5.3–5.6)
70	6.0 (5.9–6.1)
60	6.6 (6.5–6.7)
50	7.2 (7.1–7.3)
40	7.9 (7.8–8.1)
30	8.9 (8.7–9.1)
20	10.4 (10.1–10.7)
10	13.3 (12.7–13.8)

Decrease in time to ovarian failure as a function of distance from the sacral promontory to the inferior border of the ovary in the cranio–caudal axis.

CI: confidence interval.

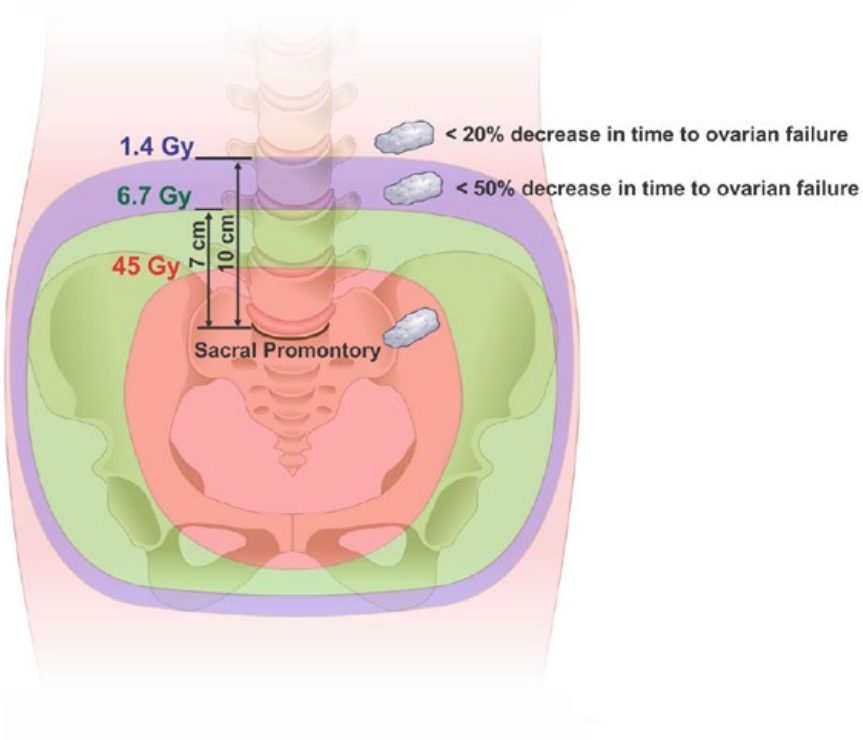


Figure 2: Schematic representation of the simulated positions of the ovaries and percentage of decrease in time to ovarian failure.

The radiation isodoses are illustrated by a classic planning of pelvic radiotherapy for cervical cancer. In it, the isodose of 45.0 Gy, 6.7 Gy, and 1.4 Gy are observed and its position in relation to the promontory. Ovaries are represented by simulating the transposition height.

DISCUSSION

Transposition of the ovaries out of the pelvic irradiation field has long been used for this purpose.[33] The general agreement appears to be as high and as lateral as possible from the original sites to be away from the pelvic radiotherapy field; however, there is no consensus concerning where to transpose ovaries. In this regard, the authors used virtual simulations to propose a practical location for the ovarian transposition in an attempt to preserve ovarian function regarding hormonal production and also fertility preservation.[34] Models are used because, in some way, they are more accessible and convenient. A model is a representation of some reality that embodies some essential and interesting aspects of that reality, but not all of it.[35]

Using a standard pelvic radiation for cervical cancer with the upper limit of the radiation fields located at intervertebral space between L4 and L5, the authors could observe that 7 cm above the sacral promontory in the caudal–cranial axis the decrease in time to ovarian failure was 50% or less. Whereas for ovaries positioned 10 cm above the sacral promontory, the decrease in time to ovarian failure would be <20%. The authors' findings are generally consistent with other studies that recommend a cranial location to ovarian transposition evaluating clinical outcomes. One study suggested an approach to transpose ovaries to a high anterolateral position at least 3–4 cm above the umbilical line and reported good results for those under 40 years old.[36] In a retrospective analysis of 53 cases, two surgical clips were applied to the upper and lower borders of each transposed ovary so that the position of the transposed ovaries could be identified. They have shown better preservation rates were obtained when the ovaries were implanted 1.5 cm above the iliac crest.[25]

Unlike that observed in the craniocaudal axis, the mediolateral or anteroposterior displacement of the simulated ovaries did not show any

difference in time to ovarian failure. One possible explanation to be considered is that the classical pelvic radiation's fields are co-planar and produce a low dose distribution that varies a little in the mediolateral and anteroposterior axis. Usually, the studies evaluating the ovarian transposition use as anatomical reference structures to be considered for radiotherapy treatment planning. The authors' study was the first to use the sacral promontory as a reference to ovarian transposition, with the potential advantage as a structure that can be easily identified during the surgical procedure. The sacral promontory is also useful in treatment planning for radiation therapy.

The present study was based on virtual simulations and did not consider any other clinical outcome. Published data confirm and generalise the concept that ovarian transposition is associated with a high preservation of ovarian function, an acceptable rate of ovarian cysts, and a low risk of metastases in the transposed ovaries.[37] The authors did not consider unilateral ovarian transposition and the results could only be applied to both ovaries located at the same distance from the sacral promontory in the cranial–caudal axis. Another important and not considered issue is the influence of the absence of the uterus in the ovarian function. It is unresolved whether it is the surgery itself or the underlying condition leading to hysterectomy that is the cause of earlier ovarian failure.[38] The results are only applicable in the scenarios of adjuvant pelvic radiotherapy and do not contemplate brachytherapy, para-aortic irradiation, or even the chemotherapy impact on oocytes damage.

The authors' study was not able to demonstrate a difference in time to ovarian failure with the three radiation techniques studied. The authors attribute that to the fact that they did not modulate the field to avoid the ovaries. Sophisticated external beam irradiation techniques, such as IMRT and VMAT, could offer by means of 'dose painting' a considerable reduction in dose to the transposed ovaries. After ovarian transposition using surgical clips, the ovaries could be identified in the planning CT and an avoidance volume created by the radiation oncologist. This can guarantee that even a lower dose of radiation will be delivered to that volume.[39]

CONCLUSION

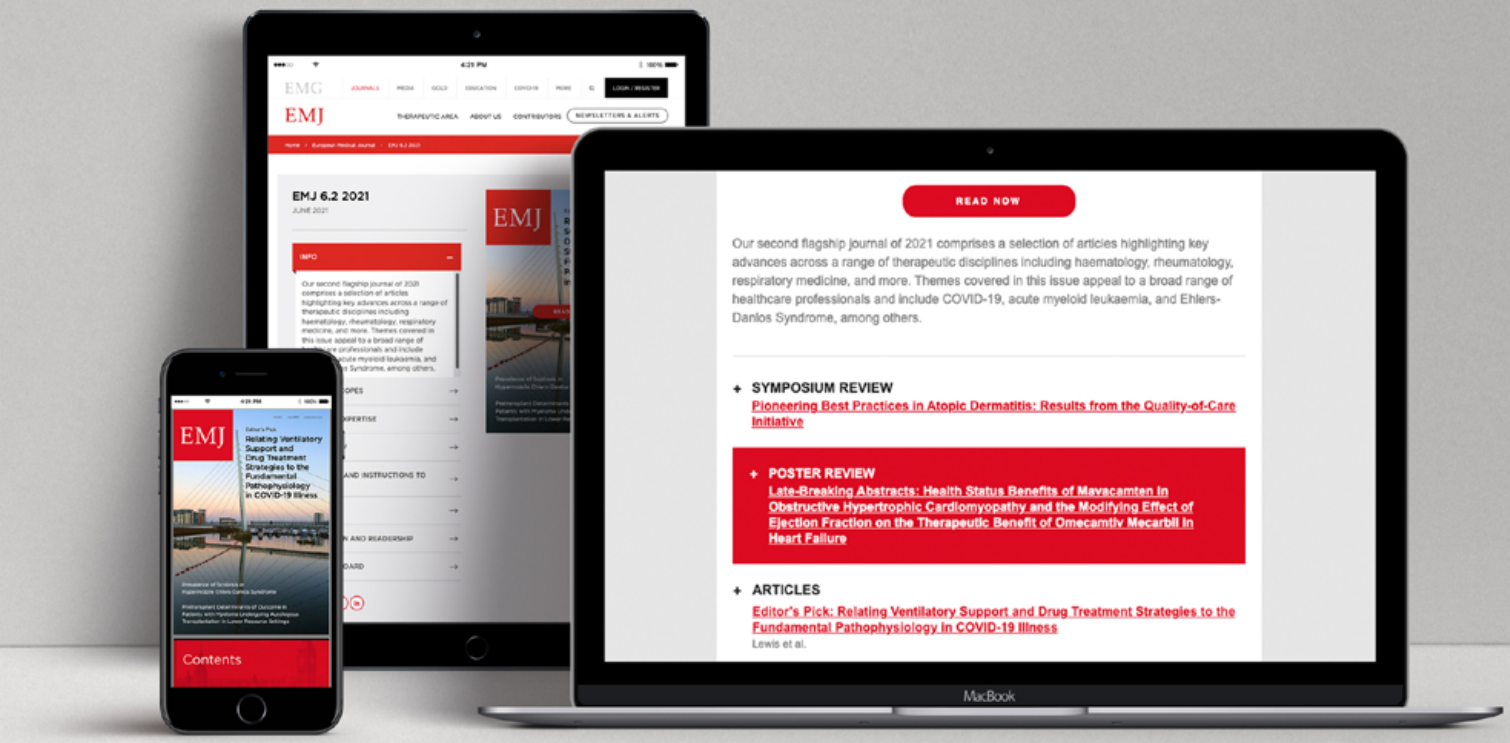
In summary, this study was an attempt based on virtual simulations to define the location of the ovaries in the ovarian transposition. The authors used the sacral promontory as the anatomical landmark for ovarian placement, which is accessible by the surgeons and radiation oncologists. A cranial distance ≥10 cm from the sacral promontory has shown a minimal decrease in time to ovarian failure. The proposed model seems to be easy to apply in clinical practice as well as to provide information for medical decision-making. These findings can potentially improve the management and counselling of patients with cervical cancer in childbearing age. More studies with clinical outcomes and follow-up of the patients are needed to validate and optimise the model proposed.

References

1. Torre LA et al. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87-108.
2. Quinn M et al. Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. BMJ. 1999;318(7188):904-8.
3. Nguyen C et al. Management of stage I cervical cancer in pregnancy. Obstet Gynecol Surv. 2000;55(10):633-43.
4. Rodriguez-Wallberg KA, Oktay K. Options on fertility preservation in female cancer patients. Cancer Treat Rev. 2012;38(5):354-61.
5. Wallace WHB et al. Ovarian failure following abdominal irradiation in childhood: natural history and prognosis. Clin Oncol (R Coll Radiol). 1989;1(2):75-9.
6. Wallace WHB et al. The radiosensitivity of the human oocyte. Hum Reprod. 2003;18(1):117-21.
7. Adriaens I et al. The current knowledge on radiosensitivity of ovarian follicle development stages. Hum Reprod Update. 2009;15(3):359-77.
8. Plante M, Roy M. Fertility-preserving options for cervical cancer. Oncology (Williston Park). 2006;20(5):479-88.
9. Shifren JL, Gass MLS; NAMS Recommendations for Clinical Care of Midlife Women Working Group. The North American Menopause Society recommendations for clinical care of midlife women. Menopause. 2014;21(10):1038-62.
10. Hinds L, Price J. Menopause, hormone replacement and gynaecological cancers. Menopause Int. 2010;16(2):89-93.
11. Michaelson-Cohen R, Beller U. Managing menopausal symptoms after gynecological cancer. Curr Opin Oncol. 2009;21(5):407-11.
12. Rossouw JE et al.; Writing Group for the Women's Health Initiative

Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002;288(3):321-33.

13. Grady D et al.; HERS Research Group. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA. 2002;288(1):49-57.
14. Koliopoulos G et al. Conservative surgical methods for FIGO stage IA2 squamous cervical carcinoma and their role in preserving women's fertility. Gynecol Oncol. 2004;93(2):469-73.
15. Lester-Coll NH et al. Preserving fertility in adolescent girls and young women requiring craniospinal irradiation: a case report and discussion of options to be considered prior to treatment. J Adolesc Young Adult Oncol. 2014;3(2):96-9.
16. Nahhas WA et al. Lateral ovarian transposition. Ovarian relocation in patients with Hodgkin's disease. Obstet Gynecol. 1971;38(5):785-8.
17. Arian SE et al. Ovarian transposition: a surgical option for fertility preservation. Fertil Steril. 2017;107(4):e15.
18. Yamamoto R et al. A study of risk factors for ovarian metastases in stage IB–IIIB cervical carcinoma and analysis of ovarian function after a transposition. Gynecol Oncol. 2001;82(2):312-6.
19. McCall ML et al. Conservation of ovarian tissue in the treatment of carcinoma of the cervix with radical surgery. Am J Obstet Gynecol. 1958;75(3):590-600.
20. Pahisa J et al. Laparoscopic ovarian transposition in patients with early cervical cancer. Int J Gynecol Cancer. 2008;18(3):584-9.
21. Clough KB et al. Laparoscopic unilateral ovarian transposition prior to irradiation: prospective study of 20 cases. Cancer. 1996;77(12):2638-45.
22. Fujiwara K et al. Subcutaneous transposition of the ovary following hysterectomy. Int J Gynaecol Obstet. 1997;58(2):223-8.
23. Gareer W et al. Needle oophoropexy: a new simple technique for ovarian transposition prior to pelvic irradiation. Surg Endosc. 2011;25(7):2241-6.
24. Hodel K et al. The role of ovarian transposition in conservation of ovarian function in radical hysterectomy followed by pelvic radiation. Gynecol Oncol. 1982;13(2):195-202.
25. Hwang JH et al. Association between the location of transposed ovary and ovarian function in patients with uterine cervical cancer treated with (postoperative or primary) pelvic radiotherapy. Fertil Steril. 2012;97(6):1387-93.
26. Moawad NS et al. Laparoscopic ovarian transposition before pelvic cancer treatment: ovarian function and fertility preservation. J Minim Invasive Gynecol. 2017;24(1):28-35.
27. Small W et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. Int J Radiat Oncol Biol Phys. 2008;71(2):428-34.
28. Wallace WHB et al. Predicting age of ovarian failure after radiation to a field that includes the ovaries. Int J Radiat Oncol Biol Phys. 2005;62(3):738-44.
29. Finney DJ, Statistics for Biologists (1980) 4th edition, London, New York: Chapman & Hall, pp.196.
30. Seber GAF, Wild CJ, "Statistical inference," Nonlinear Regression (2005), New Jersey: John Wiley & Sons, Inc., pp.191-269.
31. Bewick V et al. Statistics review 9: one-way analysis of variance. Crit Care. 2004;8(2):130-6.
32. Bates DM, Watts DG, Nonlinear Regression Analysis and Its Applications (1988), Hoboken: John Wiley & Sons, Inc.
33. Anderson B et al. Ovarian transposition in cervical cancer. Gynecol Oncol. 1993;49(2):206-14.
34. Chan JL, Wang ET. Oncofertility for women with gynecologic malignancies. Gynecol Oncol. 2016;144(3):631-6.
35. Pérez-Andújar A et al. The predicted relative risk of premature ovarian failure for three radiotherapy modalities in a girl receiving craniospinal irradiation. Phys Med Biol. 2013;58(10):3107-23.
36. Huang KG et al. A new approach for laparoscopic ovarian transposition before pelvic irradiation. Gynecol Oncol. 2007;105(1):234-7.
37. Gubbala K et al. Outcomes of ovarian transposition in gynaecological cancers; a systematic review and meta-analysis. J Ovarian Res. 2014;7(1):69.
38. Moorman PG et al. Effect of hysterectomy with ovarian preservation on ovarian function. Obstet Gynecol. 2011;118(6):127-9.
39. Ghadjar P et al. Modern radiation therapy and potential fertility preservation strategies in patients with cervical cancer undergoing chemoradiation. Radiat Oncol. 2015;10:50.



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