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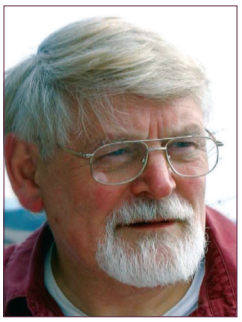

Denys Wheatley
Editor.

Oncology News – Its Future

It is with regret that Patricia McDonnell, Founder and Managing Editor of *Oncology News*, has given up publishing this journal that has run successfully for a decade. She, along with her husband Grant, have done a wonderful job in providing one of the best updating publications in cancer in the world. She had previously worked on a similar journal that did much the same for ENT specialists, but cancer is a much wider field with a far greater readership.

During all this, Patricia has had three children, and her family demands are now very high, so she decided to go back to her training in accounts with a local firm for a steadier job! As a result, there has been a hiatus since June unfortunately with neither a May/June nor a July/August issue emerging. This was largely due to much deliberation on my part in finally deciding to continue publishing *Oncology News*. But it will have to change, particularly in the printing and distribution of the hardcopy version, which in this day and age is mostly unnecessary for a journal freely accessible online. The journal will now become a partner to another cancer journal I recently created, namely *Cancer Hypotheses*, also designed as a forum for discussion on ideas about all aspects of cancer, including critical reviews of previous or extant hypotheses. It is also freely accessible online (www.cancerhypotheses.org.uk) and is a publication run by my biomedical editing company, BioMedES UK (www.biomedes.co.uk). Our *Oncology News* web manager and designer will remain with us for some time, but work will probably be transferred directly to BioMedES in 2018. It looks as if we have retained our assistant editors, reviewers, and other contributors, which is a much welcome relief. Thus while we will continue to publish updating articles on cancer, we will continue to publish notices of conferences, seminars, workshops, courses and events relevant to the field of cancer in its broadest sense, and will be glad to receive commercial advertisements as in the past. One small change will be needed to help defray the costs incurred by BioMedES, particularly at this time of transition; we will have to charge a nominal fee for all articles and contributions (£35, US$50,40 euros), but commercial advertisements will either remain in line with previous charges or can now be individually negotiated.

Oncology News has published many germaine and topical papers on a wide range of cancer issues. Submissions are particularly important to us at this juncture; I invite everyone to contribute to ensure that we continue to deliver as diligently in the future as to date. We are also keen to receive papers on proposed investigations, the setting up of clinical trials, etc., i.e. prospective as well as retrospective articles. Those of a more theoretical nature will also be considered for *Cancer Hypotheses*, if the author agrees. Like the latter journal, we would welcome the submission of some controversial papers to *Oncology News* (see below), since to date there has been little feedback. A section will be devoted to comments on our published articles and the questions they often raise.

My hope is that we can progress steadily as before, providing useful information and findings in the field of cancer, as well as being a "notice-board" of events for readers to see which conferences and workshops are in the offing. I have enjoyed my time as editor and find writing editorials challenging; however, this ensures that I keep my grey matter alive on aspects of the subject, on which I have researched throughout my entire career (and am still researching). There are always some surprises cropping up about cancer, some of which should stimulate further research. One particular article in mind is that by Söderqvist et al. relating to the possibility that even the weak Rf emitted by mobile phones increases the incidence of brain tumours, notably on the side of the head to which the person mostly holds the phone. In my editorial based on it [1], the question was raised as to whether there is any substance in this finding. However, it will be another 5-10 years before sufficient time has elapsed to gauge this matter from the statistics, inevitably because carcinogenesis induced by weak agents can take 25 years or more for tumours to become properly manifest. Hopefully we will be able to update in due course if *Oncology News* has the same longevity!

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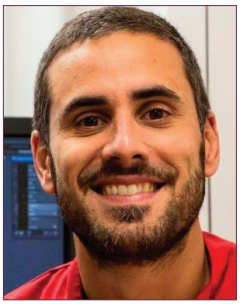
Breast cancer brain metastasis: The complex bench-to-bedside proceedings



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Advances in new strategies for cancer treatments have markedly improved the life expectancy of patients. However, therapy of secondary spread (metastasis) of tumours remains far from satisfactory; currently, metastasis of primary tumours causes 90% of total cancer deaths [1].

However, one particular tumour type – breast cancer – shows a significant increase in patient survival, life expectancy doubling in the last 40 years according to Cancer Research UK, 2015. This type of cancer has the ability to metastasise to several distant organs, such as lung, bone, liver and brain [2]. Clinical data indicates a huge variability in the incidence of brain metastases, usually in the range of 10 to 40% depending on breast cancer subtype [3]. Nevertheless, one feature is common to all of these reports, i.e. patient survival is measured in just months once cancer cells disseminate to the brain.

Part of the meagre improvement conferred by current therapies is the lack of experimental models that recapitulate accurately this multistep disease and, thus enable reliable analysis of different therapeutic approaches. We can find numerous in vitro and in vivo models in the literature for the study of different primary and secondary tumours, which can be categorised based on tumour type, animal background, tumour induction route, etc. With the caveat that each animal model carries its own advantages and limitations [4], we will describe different pre-clinical studies in which mouse models for the study of breast cancer brain metastasis have proved useful.

Mouse models in brain metastasis research

The initial stages in the design of novel therapeutic drugs comprise a thorough pre-clinical work up based on multiple in vitro and in vivo validations. In the case of brain diseases, there are several groups working on the elaboration of 3D in vitro models, in an attempt to epitomise the complex architecture of the central nervous system and the blood-brain barrier (BBB) in particular [5,6]. However, to the present day, none of these models seem to provide a sufficiently representative approach to completely replace in vivo validation. Therefore, animal models remain an inevitable tool for the study of neurological diseases and subsequent therapy development.

Although it is impossible to fully extrapolate results obtained from a rodent-based study to the actual human response, current techniques allow researchers the use of xenograft animal models. These are based on the injection of human cancer cells into immunocompromised animals, and thus represent a semi-humanised approach. This allows one to take a step closer to understanding the interactions between human cancer cells and the brain. We will describe how some of these humanised animal models have shed light on the biology behind brain metastasis progression and how this has potential clinical applications.

Molecular targeted therapy

One of the newest approaches to the treatment of cancer metastasis is molecular targeted therapy (MTT). This concept relies on the idea of targeting proteins specifically involved in tumour growth and dissemination. A particular family of transmembrane proteins that play a critical role in the successful colonisation of circulating tumour cells in distant organs are the cellular adhesion molecules (CAMs). This ubiquitous family of proteins has pivotal roles in almost all phases of human biology (such as proliferation, migration, apoptosis, survival, etc.), as well as in many diseases [7]. Despite the complexity of metastasis, which comprises a number of different stages, there is evidence that CAMs are actively involved in many, if not all, steps of the metastatic cascade [8,9].

The privileged location of CAMs on the cancer cell surface makes them attractive targets for clinical trials [10]. Two primary approaches to evaluating the potential of anti-CAM therapies have been used in our lab. The first approach involves blocking antibodies against particular CAMs that are known to be involved in tumour progression. The aim has been to block the interactions between CAMs expressed on tumour cells and their counter ligands in the tumour microenvironment [11]. The second approach has used interference RNA (iRNA) techniques to knockdown gene expression of specific CAMs so as to determine their impact on tumour progression by modulating the interaction of metastatic cells with brain cell populations [12].

Targeting different stages of brain metastasis

The design of experimental studies to investigate brain metastasis can be focused at different phases of the metastatic cascade. Some studies are aimed at treating the early stages of colonisation in the brain, whilst others have been designed to target tumour colonies once they have reached a compromising size within the central nervous system. In the first case, metastatic tumour cells are introduced into the bloodstream by intracardiac or intracarotid injection, and allowed to disseminate to the brain as would occur in patients. In the second case, tumour cells can be introduced directly into the brain by stereotaxic microinjection to bypass the initial seeding stages, and thus focus on downstream tumour proliferation within the brain environment.

Early stage diagnosis and treatments

The diagnosis of brain metastasis and subsequent treatment may vary depending on the number of metastatic colonies, total tumour volume, and their location within the central nervous system. Therefore, early diagnosis is vital to detect tumours at a size when conventional therapies, such as surgery or radiotherapy, can be most effective on tumour progression. Improvement in early diagnostic methods would give clinicians a greater window of opportunity to apply such therapies and increase patient life expectancy beyond a few months.

Inflammation is one of the hallmarks of cancer, CAMs being main contributors to its onset and progression during metastasis. These molecules are very sensitive to the presence of tumour cells and their expression is significantly upregulated in the tumour microenvironment [8,11,13]. This idea formed the basis of a number of studies exploiting the presence of different CAMs, including VCAM-1 (CD106). In several models of brain metastasis, we have been able to localise micrometastases in the brain, prior to BBB disruption, through the use of contrast agents targeting VCAM-1 that can then be detected by magnetic resonance imaging [14]. This pre-clinical work is now being translated to a Phase I/IIa clinical trial.

Following the same idea of using MTT for early diagnosis, our group is now developing new approaches to facilitate delivery of therapeutic agents to micrometastases in the brain. The BBB is a natural hurdle that stops most current anti-cancer drugs from crossing into the brain, and this is particularly a problem in the early micrometastatic stages, when the BBB is completely intact, but tumours may be more amenable to treatment if they can be accessed. We have shown that, in addition to various CAMs, the vessels associated with micrometastases express high levels of another type of protein, tumour necrosis factor receptor 1 (TNFR1), which, when activated by systemically administered TNF-like agents, provokes a disruption in BBB integrity [15]. This is selective and specific to sites of micrometastases, allowing anti-cancer drugs to access the brain parenchyma at these tumour sites. Thus, this strategy holds promise for treating micrometastases that are diagnosed early, even when the BBB is still intact. This work is currently in the late stages of pre-clinical development and will be a firm candidate for future clinical trials.

Another possibility is to target the early interactions of circulating tumour cells with the vascular endothelium, via CAMs, as a potential therapeutic strategy. Such an approach would be designed to prevent adhesion of circulating tumour cells to the cerebral vasculature and subsequent extravasation into the brain parenchyma. For instance, VCAM-1 and ALCAM (CD166) are 2 inmmunoglobulin-like CAMs intimately involved in leukocyte and tumour cell interactions with the lumen of blood vessels [11]. Their counter ligands, VLA-4 and ALCAM, respectively, are expressed in many types of tumour cells, including breast cancer cells. To explore this potential therapeutic strategy in a pre-clinical mouse model of breast cancer brain metastasis, tumour cells were pre-treated with antibodies against either VLA-4 or ALCAM. These pre-treated cells were injected intracardially into mice and allowed to disseminate to the brain. As a result of the CAM neutralisation, a significant decrease in subsequent colonisation of the brain was seen (Figure 1). The results suggest the potential for antibody therapy in patients with breast cancer at risk of suffering from brain metastasis.

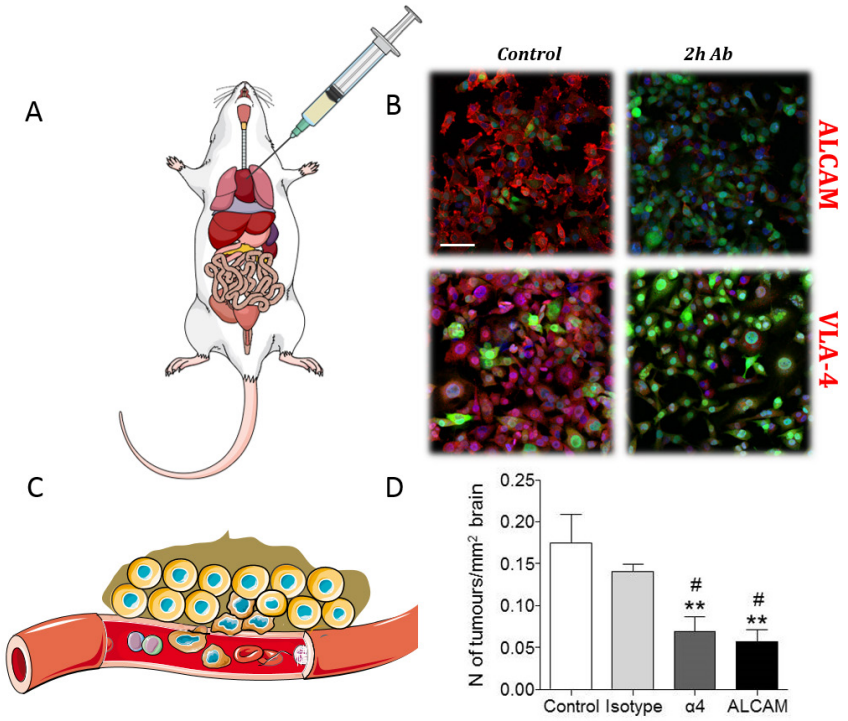

Figure 1. A. Schematic of intracardiac delivery of tumour cells. B. Illustration showing the extravasation process of circulating tumour cells into the brain milieu. C. MDA231Br cells (human breast cancer cells) in green, showing expression of ALCAM and VLA-4 (in red) before (control) and after (2h Ab) antibody treatment. A significant reduction in CAM expression is evident after treatment. Nuclei of tumour cells in blue. Scale bar 50μm. D. Graph showing significant reduction of metastatic colonies 21 days after intracardiac injection of tumour cells pretreated with neutralising antibodies compared to controls; MDA231Br cells were treated with either anti-ALCAM or anti-VLA-4 (Đ4) antibodies.

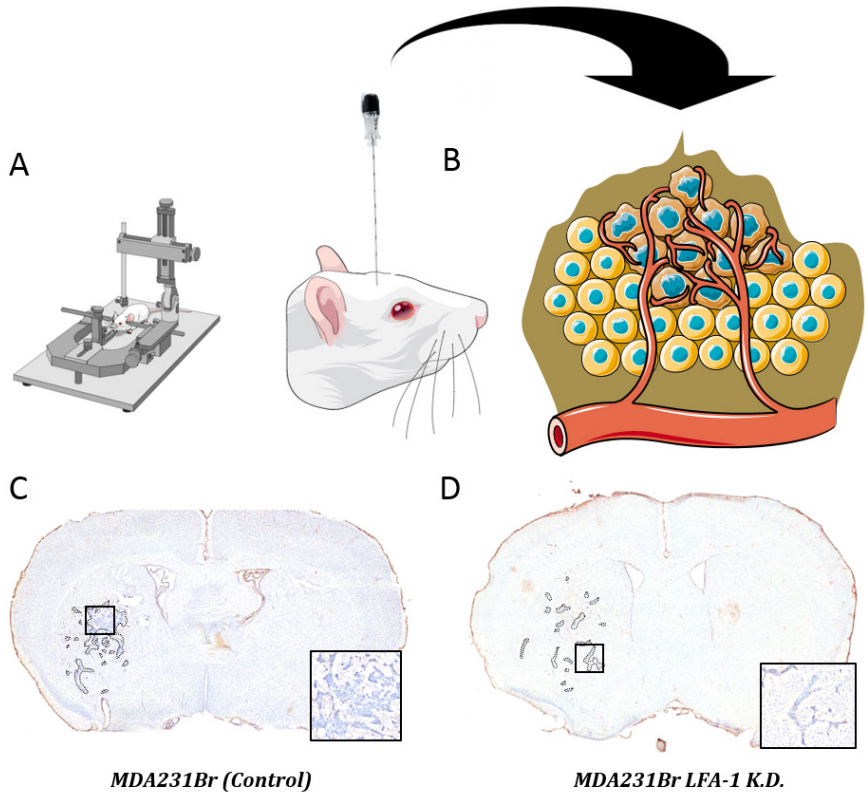

Figure 2. A. Schematic of the stereotactic frame and the intracerebral implantation of tumour cells. B. Illustration of the secondary tumour growth within the central nervous system. C-D Coronal images of mouse brain sections showing the extent of tumour colonies (dotted lines) following intracerebral injection of either parental MDA231Br cells (left) or the same cells with LFA-1 knockdown (right). A clear reduction in tumour growth was seen in animals injected with LFA-1 knockdown tumour cells compared to the control group.

Late stage treatments

A late diagnosis means that tumours are bigger and more aggressive, surgery and radiotherapy become largely ineffective, and prognosis is dismal. Usually, when patients experience signs and symptoms of primary tumours, metastatic spread is already present in different organs. Epidemiologic studies show that most cancer patients with a late diagnosis have lower chances of survival compared to patients where the treatments started in the early stages of cancer initiation (Cancer Research UK, 2016). Nevertheless, one feature of the later stages of brain metastasis growth that may facilitate treatment, despite the advanced stage, is disruption of the BBB. Thus, if more effective therapeutics can be developed/identified, then BBB disruption might well deliver such agents to the tumour microenvironment.

An important detail that must be taken into account in brain metastasis therapy is the role of the tumour/brain microenvironment. Tumour cells have the ability to manipulate the host tissue and drive it into a more tumour-supportive phenotype. As a result of this co-option of brain cell function, combination therapy targeting both the tumour cells themselves and elements of the local host response is becoming popular for the treatment of tumours in such an aggressive state. Thus, neo-adjuvant therapies, such as MTT against CAMs expressed on metastatic cells, may supplement frontline treatments (surgery or radiotherapy) and enhance patient survival.

To explore the potential of this approach, direct intracranial implantation of metastatic tumour cells into the brain has proven useful [12,16]. Some of the advantages that this model offers are the precise implantation of tumour cells into a known location and the potential to study tumour growth at later time points than is possible with the intracardiac models described above; in those models systemic dissemination of tumour cells can lead to serious deterioration in animal welfare over longer time-courses.

Using intracranial models of brain metastasis, we have shown that CAMs also play an important role in metastasis growth in the late stages of metastatic disease. Tumour cells use these proteins to interact with surrounding brain cell populations (e.g. astrocytes, microglia, neurons, endothelial cells), and blockade of certain CAM-based tumour-brain interactions has shown promising results in our pre-clinical studies [12]. We have now demonstrated that using iRNA against LFA-1 (CD11a/CD18, $\alpha L\beta 2$), another CAM expressed in human breast cancer cells, disruption in signalling with its cognate ligand ICAM-1 on brain cells significantly reduces tumour growth (Figure 2).

Translational approaches

Drug development in oncology has gained considerable momentum in the clinic. MTT, with its ability to harness the body's immune response, is also making significant progress. However, despite the large investment by industry in designing and implementing new strategies to target cancer cells, Phase I and Phase II clinical trials have a significant failure rate. One explanation for this apparent lack of success is the need for improved experimental design at the pre-clinical stage. Animal models are one of the most powerful tools to fill that gap from bench to clinic, but these do not always fully recapitulate the clinical situation. Thus, care must be taken in developing and applying these in the most appropriate and representative manner, which may involve the use of several different models. As previously described, treatments based on antibody and iRNA techniques against a particular set of CAMs show promise as new approaches to reduce brain metastasis onset and progression. The current existence of drugs against some of these proteins, such as Natalizumab (anti-VLA-4) or Efalizumab (anti-LFA1), for the treatment of other diseases, such as multiple sclerosis and psoriasis [17,18], offers the possibility of repurposing these agents for the treatment of brain metastasis. A major advantage of this approach would be access to their previous clinical history and a substantial reduction in the time taken to reach the clinic; development of new drugs varies from 10 to 17 years from inception to clinic, whilst repurposing of drugs can reduce this time to ›10 years.

Conclusions

Current treatments for patients suffering metastatic spread to the brain are based on different combinations of surgery, radiotherapy and chemotherapy. There is clear evidence for the benefit of combined,

rather than single, therapies in this situation. Our pre-clinical work suggests that CAM-based therapies may be an effective immunotherapeutic approach to target metastatic growth in the brain. The next steps will investigate the role of such agents in combination with other therapies, such as radiotherapy or chemotherapy, as a potential neoadjuvant route to the treatment of brain metastasis.

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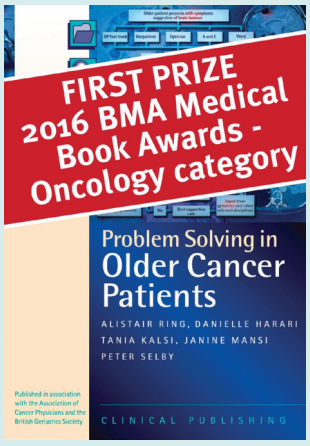
BOOK REVIEW

Problem Solving in Older Cancer Patients

Alistair Ring, Danielle Harrari, Tania Kalsi, Janine Mansi, Peter Selby. Published by: Clinical Publishing. ISBN No: 978-1-84692-110-0. Price: £39.95.



This 310 page book is published in association with the Association of Cancer Physicians and the British Geriatrics Society. The book is aimed at the Multi-disciplinary team managing the older cancer patients. I feel this book is eminently suitable for the Oncology Specialist Registrar though Consultant Oncologists, Nurses and Allied Health Professionals will appreciate it.

The numerous contributors are from the UK. The book is divided into two sections: Section One: Perspectives and Section Two Case Studies.

Section One: Perspectives, contains 18 chapters devoted to the challenges of treating the elderly cancer patient; using surgery, radiotherapy and systemic chemotherapy. Other factors such as patient selection for treatment, ethics and capacity for consent and palliative care are considered.

Section two: Case- studies comprises 32 chapters which discuss the management of a wide range of patient scenarios. For each case the case history is presented followed by several thought provoking questions. Each question is answered in detail, citing trial evidence where necessary. This is followed by a conclusion and learning points in clear bullet point format. References and examples of further reading are listed at the end of each chapter. I found that the selection of cases were typical of those seen in the out-patient clinic, for instance prostate, renal, breast, colorectal carcinomas. I felt that the decisions about treatment were balanced considering that it very easy to over treat an elderly patient and send them into an irretrievable downward spiral of complications. Experience often dictates that, "less is more."

Overall I found this text to be readable. A lot of information is presented in tables and highlighted boxes. The book revealed the importance, of involving many health care professionals including the General Practitioner in the overall management of the patient, and of good communication between the professional teams. Given the increasing incidence of cancer and that of the elderly population surviving with an increasing number of co-morbidities, I consider this to be a relevant and useful book to the Oncology Trainee in particular. It is also a useful read for other members of the oncology team.

Dr Karin Baria, Retired Consultant Oncologist.

Paving the way for personalised medicine

Why the Oncotype DX Breast Recurrence Score® test is leading the way in a new age of medicine

Nigel Bundred, MD, FRCS,
Professor of Surgical Oncology, University of South Manchester University NHS Foundation Trust.

In a consumer society with bespoke demands, broad choice and online identities, we are often told that everything is becoming more individual. Think, for example, of the 80,000 different combinations of coffee order available at Starbucks, or the huge variety of colours and features available when buying a new car.

The latest clinical approaches to medicine are no exception to this trend of ensuring that everything is tailored with maximum precision.

Traditionally, drugs have been developed to target an entire population, the so-called 'one size fits all' approach. However, such an approach fails to take into account the wide variety in responses to medicine across different patients. It is a rarely cited, yet widely accepted, scientific fact that most advanced medicines only work for a proportion of the population [1] – GlaxoSmithKline's late head of genetics, Allen Roses, once ruffled feathers by admitting that 90% of therapies are only effective in 30 to 50% of people [2].

Breast cancer is a disease which certainly requires a personal approach. Often regarded as a single disease best treated with chemotherapy, there are in fact many forms of breast cancer, all of which develop differently and require different treatment plans.

The Lancet's recent overview of the benefits of adjuvant systemic therapy found that cytotoxic chemotherapy and hormonal therapy increased disease-free and overall survival for patients with stage I or stage II breast cancer. However the picture is much more complicated than simply "chemotherapy improves survival rates": the odds of recurrence and mortality vary widely between patients with different forms of breast cancer, treated with various types of chemotherapy.

Use of chemotherapy has since been widely recommended for selected patients with node-negative breast cancer due to the high risk of distant spread and the absolute survival benefit of up to 10% [3,4].

However, between 70 and 95% of node-negative patients remain disease-free after hormone therapy alone at 10 years [5]. As such, the key is in identifying high-risk patients who may benefit from chemotherapy, and patients at low risk of recurrence who may be able to avoid the physical and emotional toll taken by such aggressive treatment. This is where the Oncotype DX® test comes into play.

Examining the expression of 21 genes in a patient's breast tumour tissue, the Oncotype DX Breast Recurrence Score test provides personalised information for tailoring treatment based on the biology of the patient's individual disease. The results of the analysis are fed into a formula that gives a number known as the Recurrence Score® result. This value – a number from 0 to 100 – can provide information about how likely the individual's breast cancer is to recur within 10 years of diagnosis and, crucially for an individual, the likelihood that the patient will benefit from chemotherapy.

Recurrence scores of 18 or less identify patients at low risk of recurrence and absence of benefit from chemotherapy. A high risk recurrence scores of 31 or more identifies women with a 1 in 5 risk of recurrence and a 28% improved survival rate with chemotherapy after surgery. The test is recommended care in four Breast Cancer International Guidelines [6] and recent data from clinical trials has confirmed its value [7].

Recommended by the National Institute for Health and Clinical Excellence (NICE) in 2013,

researchers analyse Oncotype DX test results at Genomic Health's laboratories in Redwood City, Californi

the test informs adjuvant chemotherapy decisions for patients with node-negative, oestrogen receptor positive (ER+), and human epidermal growth factor receptor 2 negative (HER2-) [8]. Through gene expression profiling, it can accurately identify breast cancer patients with a low risk of recurrence who are predicted to derive minimal benefit from chemotherapy. This personalised approach to treatment is revolutionising the way in which breast cancer – in addition to other types of the disease – is treated, and is crucial to optimising patient care.

A recent study addressed the extent to which the test has helped breast cancer patients avoid unnecessary chemotherapy. Prior to the NICE recommendation, the Breast Recurrence Score™ was evaluated in a pilot study from May to December 2012 in Greater Manchester. The study assessed both node-negative and node-positive patients who were considered as needing chemotherapy by their clinicians, with the aim of evaluating the impact of the Oncotype DX test on chemotherapy use [9]. The study assessed 201 patients treated for early stage breast cancer, all with ER+ and HER2-negative breast cancer. The Recurrence Score result had a significant impact on treatment recommendations, with only 74 patients (36.8%) receiving chemotherapy.

The remaining 127 patients (63.2%) received endocrine therapy only as their form of treatment. Testing with Oncotype DX spared two-thirds of women from unnecessary chemotherapy, a significant proportion.

Sparing patients from chemotherapy offers two major advantages. First and foremost, patients are spared an often debilitating physical toll. It is well known that chemotherapy is associated with a range of side effects which include cardiotoxicity, secondary leukaemia, hair loss and infections, as well as having a dramatic impact on quality of life. There are also psychological effects to consider. Cognitive impairment, which affects up to half of all treated women, had a huge effect on patients' working life following chemotherapy, often leading to increased absenteeism and a reduction or loss in workplace activity [10].

Patients undergoing chemotherapy treatment often rate stress as one of the emotional side-effects of breast cancer treatment [11]. Patients may feel fearful, anxious, angry, or depressed at some points during their treatment, and are striving for a sense of normality. The inability to return to work can exacerbate these problems further.

There is also an economic aspect, which is highly significant – particularly for a budget-limited NHS. Within the Manchester study, the estimated cost of chemotherapy for the patient group would have been over £1.2 million, had no testing taken place. Given that only 74 of the 201 patients underwent chemotherapy, the total cost of treatment, including the cost of the test, stood at £975,986. The total cost saving was over £250,000. This demonstrates that the Oncotype DX test not only makes clinical sense – allowing two-thirds of women to avoid unnecessary chemotherapy – but also financial sense, making the need for a personalised care approach ever more crucial.

It is important to note that the cost saving estimates contained within the Manchester study were conservative calculations, based on the list price for the Oncotype DX test. The true potential savings for the NHS are much greater, as the NHS has access to the test at a confidential price significantly lower than the published list price.

Although the test has yet to be recommended by NICE for node-positive patients, findings have shown that Oncotype DX can be equally as beneficial in such cases. For instance, a German study of patients with high-risk node-negative or node-positive disease reported a 94% disease-free survival at 5 years for patients with a Recurrence Score result of 11 or less. Once again, the Oncotype DX test was proven to reliably identify both node-negative and node-positive patients who are unlikely to benefit from chemotherapy but would have suffered the short and long-term effects of treatment .[12]

The benefits of this personalised approach to medicine are not limited to breast cancer treatment, but can be reaped across the board. Testimony to this fact is the Government's 100,000 Genomes Project that aims to bring the benefits of personalised medicine to the NHS. To seek to ensure that patients benefit from innovations in genomics, the Government has committed to sequencing 100,000 whole human genomes, from 70,000 patients, by the end of 2017. As the NHS states itself, whilst the main aim is to improve the lives of patients, there are potentially many economic benefits for the nation and the UK tax-payer also. At such a crucial time for NHS funding, such measures cannot come quick enough.

The Oncotype DX test is a key part of this changing landscape and is now becoming part of routine clinical practice in the UK. In both node-negative and node-positive patients, the test has the potential to maintain patients' quality of life and reduce the economic burden of breast cancer care. For personalised medicine, this is just the beginning.

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Role of the blood brain barrier in the development of new therapies for the treatment of brain tumours

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The blood brain barrier (BBB) refers to the membrane that exists between blood vessels and the brain, which plays a fundamental role in protecting and maintaining its privileged status. It was first described by Ehrlich in the 1880s when he injected specific dyes intravenously into animals, and found that they would stain all of the organs except for the brain. He therefore concluded that there was some special form of separation between the blood and the brain. Since then, the complexity of the BBB has been confirmed with it being described of consisting of specialised junctions and transport processes located within the membrane. In addition, there is a blood brain tumour barrier (BBTB) that is associated with tumour angiogenesis. A major challenge for neuro-oncology is to identify mechanisms by which drugs can cross the BBB to enter the brain and exert their therapeutic effects.

The BBB is composed of polarised endothelial cells connected by tight junctions in the cerebral capillary endothelium, resulting in an extremely low permeability for external molecules, including drugs. There are 5 sub-classes of membrane that combine to form the complete BBB, which include: (a) the meningeal barrier; (b) the blood-brain barrier; (c) the blood-CSF barrier; (d) the circumventricular organs, including median eminence, pineal gland, area postrema and the subfornical organ, and (e) the ependyma in the adult brain. All of these differ according to their structure, composition and location, but combine to form the complete barrier. The BBB can also be modified by events, such as inflammation, ischemia and exposure to harmful substances, by modifying its structural makeup [1].

The targeting of existing transporter mechanisms within the membranes is one approach by which drugs could enter into the brain. The transporters are normally responsible for the passage into the brain of endogenous agents such as amino acids, hormones and fatty acids. However, these may be targeted to facilitate the transfer of drugs across the BBB. For example, the OAT transporter, which normally transfers small organic compounds across the membrane, has also been reported to transport drugs such as aspirin and ibuprofen into the brain. Furthermore, the drug L-DOPA, which is used for the treatment of Parkinson's disease, has an amino acid structure that allows it to enter entry via the amino acid transporter LAT1.

Receptor-mediated transcytosis refers to the binding of molecules to the specific components of the epithelial membrane of the BBB [2]. This involves the targeting of ligands, endogenous proteins or antibodies directed against cell surface receptors (e.g. transferrin or insulin receptors) to induce receptor-mediated transfer of drugs and small peptides across the BBB. However, the therapeutic success of such a strategy will require a much greater understanding of the expression of cell surface proteins if one is to selectively target the BBB membrane.

In addition to targeting the endogenous transport mechanisms, a number of alternative approaches are being developed to facilitate drug entry into the brain:

- The first is based on the direct injection of a drug into the site of the tumour. This is an invasive surgical procedure with associated risks. There are additional problems, including diffusion of the drug from the site of injection with potential damage to the brain tissue surrounding the tumour. This can be difficult to predict depending on the heterogeneity and density of the tumour mass. Reflux of the drug solution upwards along the side of the injection cannula will have similar effects.
- A new procedure, termed convection-enhanced delivery, is more accurate for the delivery of molecules to a specific site, with particular accuracy and minimal collateral damage due to diffusion.
- Another invasive procedure being developed is the permeabilisation of the BBB via nasal mucosal engrafting [3]. This procedure exchanges the normal mucosal membrane with one that is more permeable, which allows larger molecules to cross into the brain following nasal administration. However, this is still at the experimental stage and, as it is an invasive surgical procedure, its efficiency will need to be compared with existing surgical techniques and non-invasive approaches.

Physical approaches have been used to modify the structure of the BBB to establish transient permeabilisation to allow drug entry [4]. These include ultrasound disruption, reverse osmotic opening and electrical stimulation, all of which

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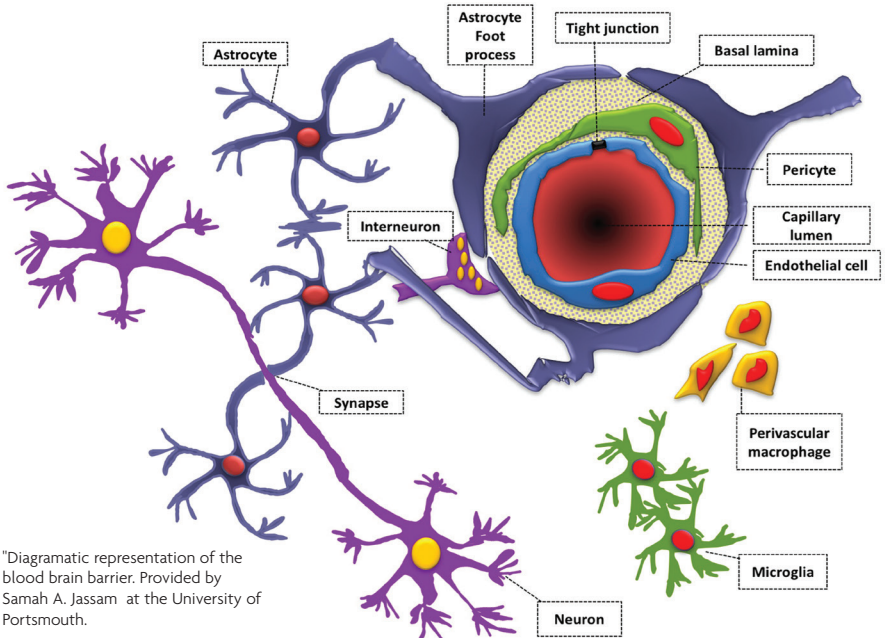

"Diagramatic representation of the blood brain barrier. Provided by Samah A. Jassam at the University of Portsmouth.

will impact on the membrane structure and function. The combined use of ultrasound with microbubbles has also been proposed as a tool for delivering drugs across the BBB. This can be used directly for drug delivery, with the drug being contained within the microbubble vesicles, or indirectly by modifying the property of the membrane to allow drugs to cross the membrane directly. Microbubbles are 1-5μm sized gas-filled vesicles containing phospholipids, proteins or polymers. Their ability to cross the BBB following ultrasound stimulation depends upon both their composition and the frequency being used. The nature of the ultrasound will also serve to localise the effect and therefore minimise damage to surrounding tissues. A clinical study is currently underway to assess the use of this technique to deliver the chemotherapeutic agent doxyrubicin to the site of a glioblastoma [4].

There is increased interest in the direct use of carriers to enable drugs to cross the BBB. Nanoparticles (NPs) are colloidal carriers that can have a natural or synthetic origin, varying in size from 1 to 1000 nm [5]. Synthetic NPs may be prepared from polymeric materials such as poly(ethylenimine) or from inorganic materials such as gold or silicon dioxide. They can also be generated from natural polymers, e.g. polysaccharides, amino acid polymers or proteins. The carriers act by adsorbing, entrapping or covalently binding the drugs. Encapsulation of drugs into NPs can target specific transport processes to enhance their entry through the BBB. A combination of the NP constituents, their size and shape will influence whether they can mediate penetration across the BBB. While the majority of studies to date have been carried out on spherical nanoparticles, other studies have been investigating the potential of other forms of particle since their synthetic nature provides an excellent opportunity to modify their shape and size. For example, polysterene NPs with a rod-shape coated with an antibody against the transferrin receptor showed a 7-fold increase in brain accumulation compared to their spherical NP counterpart. However, inorganic NPs have disadvantages because they may not be degraded or eliminated through the kidneys, leading to potential toxic side effects associated with their pharmacokinetic profile.

Another form of nanoparticles are liposomes, which are synthetic vesicles with a phospholipid membrane that self-assemble into various sizes and shapes within an aqueous environment [6]. However, liposomes may have limitations associated with the activation of the host immune system, thereby increasing their toxicity. While inorganic polymeric nanoparticles may have better stability than liposomal systems, their biocompatibility and long-term potential safety remain concerns. Both of these delivery systems have been used to deliver different types of drugs into the brain, but further development is required before the most appropriate system can be identified for routine clinical use.

Exosomes are naturally-occurring small intracellular membrane-based vesicles containing various types of lipids and proteins involved in several biological and pathological processes. They are non-immunogenic and therefore have advantages compared to other nanoparticulate drug delivery systems [7]. They can be described as bilayer membrane "nanospheres" generated and secreted by all cell types, and are found in most body fluids. They can be isolated from extracellular fluid by density gradient centrifugation and then filled with specific drugs. Because of their membrane composition, exosomes can be used to facilitate the transfer of drugs across the BBB. Studies using exoxomes derived from the U-87 glioblastoma cell line have demonstrated the encapsulation of drugs, such as paclitaxel and doxorubicin, which can be incorporated into exosomes that then cross the BBB (as shown in a zebrafish model).

Due to the cost of using *in vivo* models to assess the potential of drugs to cross the BBB, a number of *in vitro* and computational models have been developed to mimic the BBB and predict if, and indeed how, molecules may cross into the brain [8]. An appropriate model should allow for a detailed study of the role of the molecular processes that maintain membrane homeostasis, in conjunction with a demonstration that the model recapitulates the properties of the membrane in vivo, including the expression of appropriate transporter systems. One example is the development of a 3D model comprised of relevant human cell types and basal laminar proteins cultured in 24-well plates with polycarbonate membrane transwell inserts [9]. Systems can also be developed that model changes occurring in a number of disease states and therefore will be more accurate in their predictions of drug penetration into the brain. Other tools under development include in silico models, isolated brain microvessels, microfluidic models and 3D extracellular matrices-based scaffolds. All have their limitations and it is likely that a combination will be needed to fully model the *in vivo* situation.

While the BBB provides a particular challenge for the treatment of brain tumours, an increasing number of tools are being developed that hold promise for the delivery of therapeutic agents to the site of the tumour, and therefore increase the range of available therapies.

UKCRC Tissue Directory and Coordination Centre

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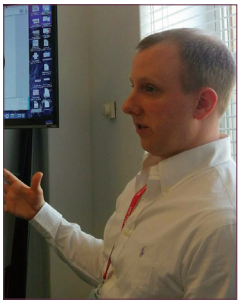

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The UK Clinical Research Collaboration (UKCRC) Tissue Directory and Coordination Centre (the Centre) aims to coordinate Biobanking activities in the UK. The Centre represents a first step in integrating national biobanking infrastructure to support research activity. You can read more about the project and how to get involved at https://www.biobankinguk.org .

A joint vision

Biomedical researchers rely on human tissue samples for a multitude of research projects; cancer is of particular note as it such a heterogeneous disease. Given the development of precision medicine and the need for more reliable disease models in other fields, the demand for high quality samples and associated data will increase over time. Until now, there has been no coordinated effort to catalogue or coordinate human biosample acquisition and storage. The Centre was established in 2014 by the UK Clinical Research Collaboration (UKCRC) Experimental Medicine Funders Group in order to achieve their Vision for Human Tissue Resources.

The funder's vision

"Funders aim to maximise the value of human tissue samples and resources while minimising duplication of effort. This requires better characterisation of tissue samples, asking for generic consent, and increased linkage to accurate clinical data. Sample collections must then be made more easily discoverable and accessible for use in high quality, ethical research."

The Centre has therefore been established to promote best practice, harmonisation and standardisation, and increase sample visibility in the hope that this will lead to increased sharing of samples, creating a more efficient research environment in the UK.

The UKCRC Tissue Directory

Launched in 2016, the UK-wide Tissue Directory, is a first step in promoting access to samples for research. The directory contains the details of biological samples and data held across >80 biobanks in the UK. The directory aims to facilitate communication between researchers and biobanks, providing a quick and efficient route for researchers to access appropriate samples and data to match their research needs.

Researchers can search the online directory and locate appropriate tissue samples held by a specific biobank, based on the associated datasets giving age and gender of donors, and sample type. It is possible to search the directory using the specific disease term by viewing the list of diseases or the A-Z of Biobanks.

The Centre does not facilitate sample access; it acts as a platform for promoting visibility of existing resources.

An ethical duty to share

The UK Ethics Committee Authority (UKECA) has now made registration in the UKCRC Tissue Directory a condition of the Research Ethics Committee (REC) favourable opinion for research tissue banks (RTB). Patients gift their samples, under the impression that they will be used for scientific medical research. This change in the terms of REC favourable opinion should lead to a shift in the culture of research. Dr Philip Quinlan has said: "It is fantastic that the UKCRC Tissue Directory and Coordination Centre has been recognised as the best centre to do this work; tissue banks will have an ethical obligation to ensure their sample collections are visible to the community and we hope this will lead to better coordination between biobanks ensuring more samples are contributing directly to medical progress." Indeed, this is the first ever defined expectation for researchers to register the existence of the samples they hold.

Award winning engagement

The Centre actively engages with all stakeholders through events, campaigns and communications to ensure the development of the project provides plenty of information. The centre works with people and organisations to promote best practice, governance and public engagement.

The Centre has run a number of successful road-shows at institutions around the country to promote its work and encourage feedback. The Centre's most recent annual meeting was held on the 16th November at the Oval in London. UK Biobanking Showcase was a unique opportunity to bring together all stakeholders in the field and featured debates, give talks and award the prestigious "Biobank of the Year".

2016 saw the centre in parliament at a Biobanking event: "The Biobanking time-bomb; maintaining public trust in medical research". The aim of this event was to address the future risks to biobanking if certain issues were not addressed. These risks include the reducing contributions from Research grants to Biobanks, cost recovery being insufficient to recover financial deficits, particularly due to the increasing cost of running

biobanks. Reward mechanisms and access to clinical data are also important issues that were discussed. Find out more about the event on our website.

As well as engaging with Biobanks and policy makers, The Centre has an active public engagement programme. Project and Engagement manager, Jessica Sims, has developed a Board game to explain biobanking to the public. This innovative approach to a complex and sensitive issue has won public engagement awards in the past. Ms Sims says "public understanding is vital to tissue donation. I wanted to develop a way of really engaging with people in a format they can understand". Contact Ms Sims at j.sims@ucl.ac.uk to learn more about the game,

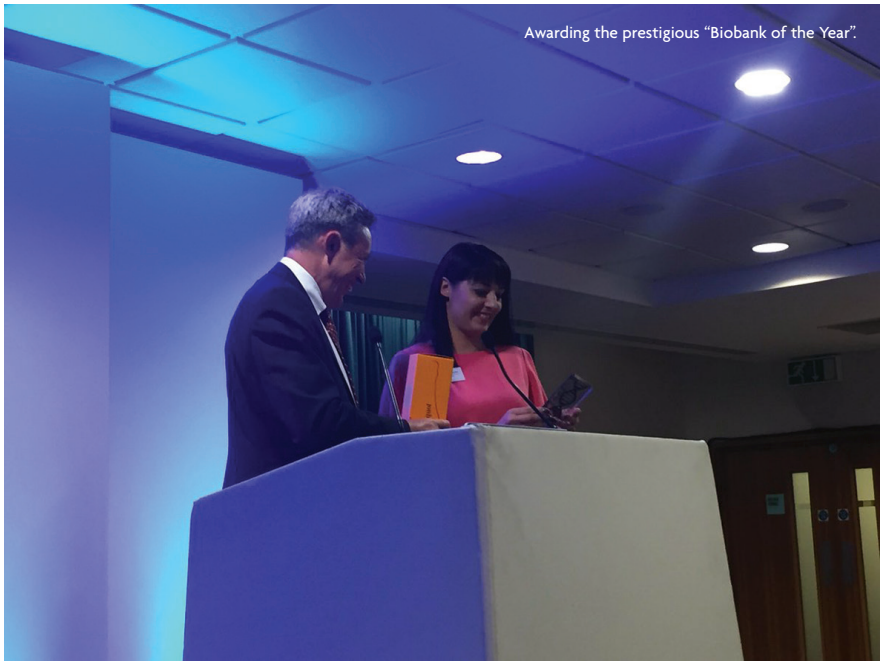
BBMRI.uk

The Biobanking and BioMolecular Resources Research Infrastructure (BBMRI) – European Research Infrastructure Consortium (ERIC; BBMRI-ERIC) – is one of the largest research infrastructures for health in Europe today. It provides services and expertise for its members, including expert centres, events, and a European sample locator. They have also coordinated a number of research projects within Europe and beyond.

The Centre represents the UK and engages with this network on ethical, legal and societal issues (ELSI), IT and Quality common service groups. It has also contributed to the drafting of sample quality standards along with BBMRI-ERIC. Visit their website or get in touch to find out more about getting involved with this network.

To get involved

The Centre in the UK relies on the research community to shape our work; it is therefore keen to engage with pathologists, particularly those involved in biobanking on how you can help (contact email at head of paper). You can register your samples online at https://directory.biobankinguk.org/ There are more resources including the latest biobanking news and advice at https://www.biobankinguk.org/. Finally, you can also Sign up to The Centre's Newsletter for all the latest news and events.



Awarding the prestigious "Biobank of the Year".

Playing the game.

Newcastle Roadshow

Hepatocellular carcinoma surveillance: A path to better effectiveness

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Worldwide, hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality and the fifth most common malignancy [1]. The highest rates of HCC occur in East Asia and Africa, given high rates of endemic hepatitis B virus (HBV) infection. In the United States and Europe, HCC most commonly occurs in the setting of hepatitis C virus (HCV) cirrhosis, although an increasing number of HCC cases are now related to underlying non-alcoholic steatohepatitis (NASH). Although the incidence of HCC in the US and Europe is lower than Asia and Africa, its incidence in the Western World is rapidly rising [2]. In fact, HCC had the largest increase in incidence among all solid tumours during the last 10 years as assessed by Surveillance Epidemiology and End Results (SEER).

HCC Surveillance

Prognosis for HCC is primarily dependent on tumour stage at diagnosis. Patients with HCC detected at an early stage qualify for curative treatments including liver transplantation, surgical resection, and local ablative therapies, yielding 5-year survival rates of ~70% [3]. However, patients presenting with advanced stage disease are only eligible for palliative treatments, with a median survival of less than one year [4]. Given the marked difference in treatment options and overall survival between early and advanced tumour stage, early HCC detection efforts are critical. Accordingly several professional societies including the National Comprehensive Cancer Network (NCCN), American Association for the Study of Liver Diseases (AASLD) and Veterans Administration (VA) recommended HCC surveillance using abdominal ultrasound with or without alpha fetoprotein (AFP) in patients with cirrhosis [5,6].

HCC surveillance fulfills all WHO criteria for implementing a cancer screening program: 1) HCC disease burden is an important health problem, 2) there is an identifiable target population, 3) surveillance is accepted by patients and providers, 4) it is affordable, 5) it achieves an acceptable level of accuracy, 6) there are standardised recall procedures, 7) there is an advantage of treating occult HCC, and 8) surveillance reduces mortality [7]. The most compelling evidence supporting HCC surveillance comes from a randomised controlled trial (RCT) with >19,000 HBV carriers in China, in which HCC surveillance facilitated higher proportions of early tumour detection (61 vs. 0%, $p<0.001$) and lowered mortality by 37% (mortality rate ratio 0.63) [8]. There is no similar level I evidence supporting surveillance among patients with cirrhosis (the primary at-risk population in the Western World), and data from the China RCT among HBV patients cannot be directly applied to cirrhosis patients due to a greater competing risk of non-HCC mortality and a lower sensitivity of surveillance ultrasound in a nodular liver [9]. However, several cohort studies have suggested cirrhosis patients undergoing surveillance have improved survival, after adjusting for lead-time bias, compared to those not undergoing surveillance [10-12]. A recent meta-analysis of surveillance-related cohort studies concluded HCC surveillance is associated with significant improvements in early tumour detection, receipt of curative therapy, and overall survival in patients with cirrhosis [13]. While an RCT would still be the ideal study design to assess surveillance benefits and harms in patients with cirrhosis, some contend that this would be difficult, if not impossible, to conduct due to ethical concerns of a non-surveillance arm [14]. While we live in an era of evidence-based medicine, a lack of randomised data does not equate to a lack of efficacy. Currently, the preponderance of data suggests HCC surveillance can improve early detection and reduce mortality. Observing these benefits in clinical practice is dependent on HCC surveillance utilisation rates and the effectiveness of surveillance tests [15].

HCC surveillance utilisation

Currently, HCC surveillance is performed in >20% of patients with cirrhosis in the United States, with lower rates among non-Caucasians, those of low socio-economic status, and patients followed by primary care providers compared to those seen by gastroenterologists [16,17]. Underuse of HCC surveillance is associated with higher rates of advanced tumour presentation, when treatment options are limited and survival significantly worse [18]. The most common reason for surveillance not being performed is due to a lack of orders from providers [19]. This deficit can be related to several issues including difficulty with recognising at-risk patients, lack of knowledge about HCC surveillance benefits, and clinic time constraints given the myriad of competing medical issues [20]. Patients typically demonstrate high levels of knowledge about HCC surveillance and report

high levels of acceptance and willingness to participate in HCC surveillance [21]. A study conducted in a safety-net patient population suggested patient-reported barriers, such as lack of transportation and difficulty scheduling surveillance testing, may be associated with lower rates of surveillance, but it is unclear if the data can be generalised to non-safety-net settings [22].

HCC surveillance effectiveness

The primary modality for HCC surveillance is an abdominal ultrasound, which has many advantages including being: readily available, safe, inexpensive, and non-invasive with no risk of radiation or contrast exposure. Sensitivity for early stage tumours ranges from 29 to 100% in prospective cohort studies, with a meta-analysis demonstrating a pooled sensitivity of 63% (95%CI: 49-76%) in patients with cirrhosis [23]. However, data suggest its effectiveness for early detection is substantially lower, with a sensitivity of ›50% [24]. Furthermore, ultrasound can be associated with false positive or indeterminate results in over one-fourth of patients, leading to physical and financial harms from diagnostic evaluation, as well as possible psychological harms, including patient anxiety [25]. Lower effectiveness of ultrasound in clinical practice could be related to several reasons including its operator dependent nature and differences in patient populations including higher rates of obesity or more advanced fibrosis. Limitations of ultrasound sensitivity may worsen in the future as the epidemiology of HCC shifts to NASH-related, given lower image quality in patients with obesity and NASH-related cirrhosis [26]. Use of cross-sectional imaging, such as MRI, is associated with increased sensitivity and specificity for early tumour detection; however, this strategy would not be cost-effective if applied to all at-risk patients [27].

"Underuse of HCC surveillance is associated with higher rates of advanced tumour presentation, when treatment options are limited and survival significantly worse."

Using biomarkers in combination wth ultrasound could potentially improve early tumour detection. In the prior meta-analysis of prospective cohort studies, using AFP with ultrasound raised sensitivity for early HCC to 69% (95%CI 53-81%), although this difference was not statistically significant [23]. Subsequent studies have been more optimistic about the potential value of adding AFP to ultrasound, demonstrating significant increases in sensitivity for HCC detection. A study among 1597 patients followed for a median of 4.8 years found the sensitivity for any-stage HCC detection increased from 92 to 99.2%, with minimal loss in specificity when adding AFP to ultrasound for surveillance [28]. Similarly, another cohort study among 442 cirrhosis patients found adding AFP increased sensitivity for any-stage HCC detection from 43.9 to 90.2% and sensitivity for early HCC detection from 31.7 to 63.4% [24]. Furthermore, most data on the benefit of adding biomarkers has evaluated their utility as a one-time test at a specific cut-off, although providers often account for changes in biomarker values when interpreting data in clinical practice. Longitudinal changes in AFP measurement can have greater accuracy for early HCC detection, but they still require further evaluation as how best to be implemented in a standardised fashion [29,30].

How can we improve?

As discussed above, HCC surveillance has the potential to improve early detection and survival in patients with chronic hepatitis B and cirrhosis; however, the full benefits of HCC surveillance are not seen in clinical practice. Fortunately, there are several ongoing efforts to optimise surveillance effectiveness in the future.

For HCC surveillance utilisation, interventions, such as provider reminder systems and mailed outreach strategies, have shown potential to significantly improve HCC surveillance rates. A quasi-experimental study evaluating a point-of-care clinical reminder for HCC surveillance targeting primary care providers within the VA health system demonstrated increased surveillance rates from 18.2 to 27.6% ($p<0.001$); however, the rate in the intervention arm still failed to reach the minimum cut-off at which HCC surveillance becomes beneficial [31]. A recent study using mailed outreach invitations in a racially diverse socio-economically disadvantaged patient population increased HCC surveillance uptake from 24 to 45% [32]. This strategy was equally effective among all subgroups of patients including Caucasians or non-Caucasians, documented or suspected cirrhosis, and those receiving or not receiving gastroenterology care. However, further follow-up is needed to determine if high repeat surveillance rates can be maintained through this strategy given prior studies suggesting possible screening fatigue over time.

For HCC surveillance test effectiveness, recent studies have also shown promise in using biomarker panels, such as the GALAD score, for improving sensitivity for early tumour detection [33]. Currently, several prospective efforts including the Early Detection Research Network (EDRN) Hepatocellular Early Detection Strategy (HEDS) study are also underway to identify and evaluate novel surveillance biomarkers to improve sensitivity for early detection [34].

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[^{18}F] Fluoromisonidazole PET in Rectal Cancer – a short review

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The World Health Organisation (WHO) predicts that the number of incidences of colorectal cancer worldwide will rise to 1.36 million for men and 1.08 million for women by 2035 [1]. Hypoxia in cancer cells leads to radioresistance [2,3]. One way to improve personalised radiotherapy involves targeting hypoxic regions within the tumour. Strategies to successfully identify hypoxia in rectal cancer have repeatedly failed due to the inability to distinguish tumours with severe or non-resolving hypoxia. Thus, it is crucial to develop non-invasive biomarkers of tissue hypoxia in such tumours through imaging. The invasive method of Eppendorf electrode [4] is considered the gold standard for measuring oxygen distribution in tumours and has been shown to correlate with response to RT. However, positron emission tomography (PET) is an imaging technique used to visualise and quantify pathophysiological processes of interest (for example, glucose metabolism or hypoxia) within a tissue via administration of a radiopharmaceutical (commonly known as tracer). [^{18}F]fluoromisonidazole ([^{18}F]FMISO) is a radiopharmaceutical used to identify hypoxia in various tumour types. Increased retention of [^{18}F] FMISO in tumour cells is suggestive of hypoxia and vice-versa. Therefore, the aim was to explore changes in [^{18}F]FMISO PET imaging parameters in human rectal tumours before and after 8-10 fractions (~2 weeks) of chemoradiotherapy (CRT) to predict clinical response.

Data Acquisition

Patients were recruited within an ethically-approved prospective observational study: modulation of *R*adiotherapy according to *HY*poxia: exploiting changes in the *T*umour *M*icroenvironment to improve outcome in rectal cancer (RHYTHM). All patients provided written informed consent for the study procedures. Patients with histologically confirmed invasive adenocarcinoma of the rectum having neoadjuvant chemoradiotherapy (CRT) (45Gy in 25 fractions over five weeks plus capecitabine chemotherapy (900mg/m^2 twice daily)), prior to planned curative rectal resection were recruited between October 2013 and April 2016. Patients were imaged on PET-CT between 0 and 45min, at 2h and 4h, both at baseline and two weeks into CRT. The patient cohort was divided into two groups. The first six patents did not receive an enema before the 4h PET-CT and were called the non-enema group. The last four patients received an MICROLAX® micro-enema before the 4h scan, called the enema group.

Image Analysis Methods

The tumour regions of interest (ROI$_{tumour}$) were manually delineated on magnetic resonance (MR) scans and transferred to the PET-CT using rigid registration in Eclipse radiation treatment planning software (Varian Medical Systems (version 10), Inc, Palo Alto, CA, USA). The ROI$_{tumour}$ were transferred to PMOD (PMOD Technologies (v3.6) Ltd., Zurich, Switzerland) to ensure exclusion of the bladder region using semi-automatic thresholding. All ROIs were propagated to the earlier scans using rigid registration in PMOD for the time series analysis of the PET data. Tumour-to-muscle (T:M) SUVmax and tumour-to-blood (T:B) SUVmax was used to analyse static PET images at 4h. The 0-45min dynamic PET scans were analysed using the Casciari pharmacokinetic model [5] to report relevant parameters including, hypoxia (Ka) and perfusion (F). American Joint Committee on Cancer (AJCC) 7.0 [6] was used to report pathological tumour regression grading and Shapiro-Wilk normality test was used to test the data normality.

Results and Discussion

Eight patients underwent total mesorectal excision. Five of the eleven patients were classed as good responders (AJCC 0/1 or good clinical response) and six as poor responders (AJCC 2/3 or poor clinical response). The median T:M SUVmax was 2.14 (IQR: 0.58) at baseline and decreased by 33% by two weeks. The corresponding median tumour hypoxia volume was 1.08 (IQR: 1.31) cm^3 and decreased by 95% by two weeks. The median T:B SUVmax was 2.46 (IQR: 1.50) at baseline and decreased by 29% by two weeks. The corresponding median tumour hypoxia volume was 5.68 (IQR: 5.86) cm^3 and decreased by 56% by two weeks. Using Casciari modelling, the median tumour F was 4.10 (IQR: 1.71) millilitres/grams/min (mlg^{-1}min^{-1}) at baseline and decreased by 29% to 2.48 (3.62) mlg-1min-1 by two weeks. In nine of the eleven patients scanned at baseline and two weeks into CRT, tumour perfusion decreased post-CRT in non-responders and increased in responders, except in one patient (Figure 1). The alterations in tumour perfusion trend with its response highlights the importance of changes in vasculature-related functional parameters during radiotherapy, its important role in understanding hypoxia, and its relation with outcome. None of

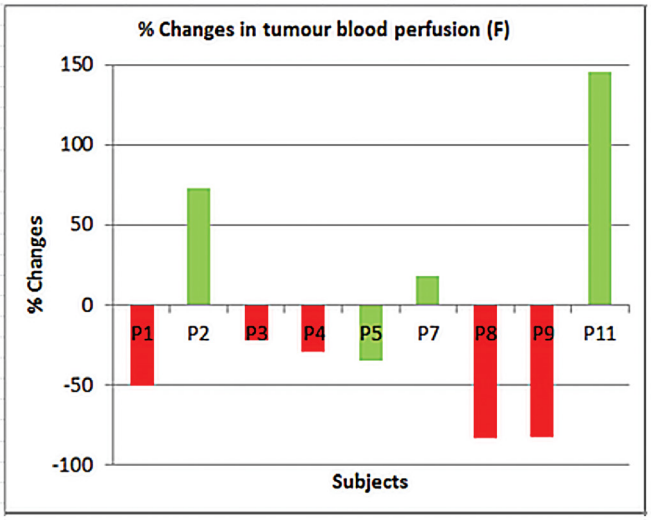

Figure 1: Percentage changes in tumour blood perfusion between baseline and after 2-weeks into chemoradiotherapy from fitting 0 to 45 min [^{18}F]FMISO PET data to the Casciari model in rectal cancer patients. The red bars show non-responders and green bars responders. [^{18}F]FMISO=[^{18}F]fluoromisonidazole; PET=positron emission tomography.

the other changes in PET imaging parameters between baseline and two weeks showed any clear trend with clinical outcome; see Greenhalgh et al. [7] and Puri et al. [13] for details.

At baseline, tumour F showed a weak relationship with T:M SUVmax and T:B SUVmax at 4h and none after two weeks of CRT, suggesting that these parameters from static PET may primarily exhibit chronic hypoxia. The Ka had a poor relationship with T:M SUVmax and T:B SUVmax at baseline and after two weeks of CRT, suggesting that the semi-quantitative and quantitative methods of measuring hypoxia from static and dynamic PET, respectively, are not equivalent.

There are two major challenges that affect the interpretation of [^{18}F]FMISO PET results in rectal tumour, including, but not limited to, the rate of renal excretion to the bladder, the activity concentration within the bladder and rectal lumen, their volumes at the time of imaging, their proximity to the tumour, the time the patient empties the bladder, how quickly the bladder refills, how well the enema works, the attenuation correction, and other factors.

1. Bladder Activity Accumulation: Accumulation of [^{18}F]FMISO in the bladder starts 10-15 min post-tracer injection due to urinary excretion at variable rates. This leads to a high activity concentration within the bladder by the end of the study (Figure 2) that can affect both delectability and quantification of the lesion due to a phenomenon called spill-in. Figure 3 shows a schematic diagram of the phenomenon of spill-in count from bladder inside the tumour due to scatter and random photons. The false lines of responses are accepted as true events, leading to an overestimation of activity in the surrounding region and causing an error. Tumour regions within very close proximity of the bladder also get further affected during image reconstruction by the spill-in of activity from bladder due the limited spatial resolution of the PET scanner. Catheterization of the bladder has been suggested, but it is uncomfortable for the patients and a potential source of infection. A comfortably full bladder is normally required for rectal cancer radiotherapy. Frusemide may be considered as aiding rapid urinary excretion and diluting the residual radioactivity in the bladder, but its feasibility has to be assessed. Another solution may be to reconstruct the PET images by restricting the counts from the bladder [8], but it is too early to see how this will be translated into the clinic.
2. Rectal Activity Accumulation: [^{18}F]FMISO is excreted through the biliary tract into the gastrointestinal tract as well as through the urine. When the rectal lumen contains high [^{18}F]

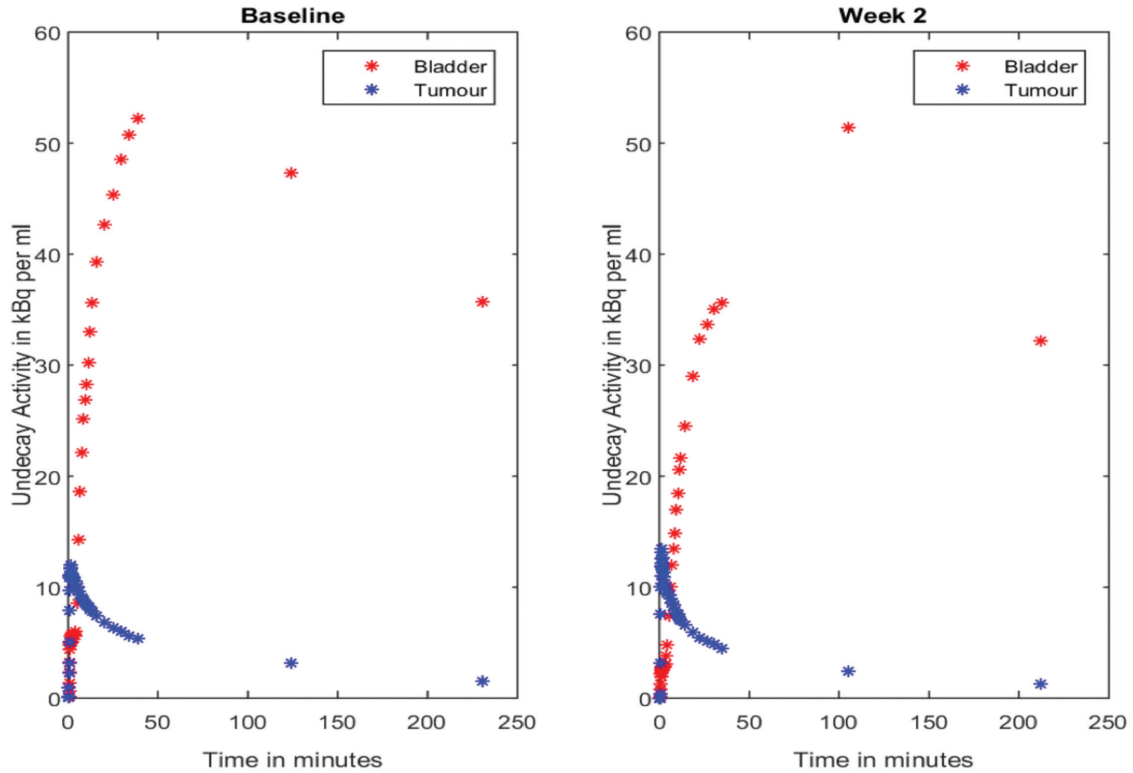

Figure 2: The undecay corrected averaged time activity curves of [^{18}F]FMISO PET at the bladder and tumour at baseline (in A) and after 8-10 fractions of chemoradiotherapy (in B) between 0 and 4h. Bettinardi et al [11] assessed random and scatter characteristics over a range of 0-60 kBq/ml within the PET field of view. However, it should be noted that we found a much higher activity concentrations (undecay corrected activity of up to 150kBq/ml directly related to random and scatter events) within individual human bladder that would lead to an increase in random and scatter in a non-linear fashion.

FMISO activity and is within close proximity to the tumour, the spill-in of activity from rectal lumen into the tumour is unavoidable due to the limited resolution of the PET scanner. The use of an enema prior to the 4h scan reduced this non-tumour luminal activity (Figure 4).

[^{18}F]FMISO is not taken up by the tumour in large amounts compared to other hypoxia tracers, leading to a lower tumour to background contrast. The PET tracers that show clearance to bladder or colorectal lumen may have similar issues for other tumours in the pelvic region, such as cervix and prostate cancer. A recent review [9] and two other studies [10,11] suggest similar difficulties with [^{18}F]FMISO PET in rectal cancer, but they did not take steps to mitigate these issues. Of these challenges, some are solvable, such as by using an enema to reduce spill-in from non-tumour accumulation of [^{18}F]FMISO. However, the problem of spill-in from bladder has not currently been solvable and may require considerably more investigation. Another PET study using ^{68}Ga-PSMA-11 in prostate cancer [14] suggested severe artefacts surrounding the bladder and the kidneys in PET images that are frequently used in clinical practice, and has investigated the impact of these artefacts on tumour quantification. They concluded that inaccurate scatter correction methods currently used in clinical routine tend to overestimate the scatter contribution.

Conclusion

This pilot study with only a small sample size does not support the hypothesis that a reduction in [^{18}F]FMISO uptake in rectal cancer is predictive of clinical response. There are two main problems, namely spill-in from non-tumour activity in the rectum, and from the bladder into the environs of the tumour. Careful consideration should be given to PET acquisition and reconstruction to minimise spill-in counts from the bladder. This preliminary review indicates fundamental difficulties in the interpretation of [^{18}F]FMISO PET for rectal cancer, limiting its clinical applicability.

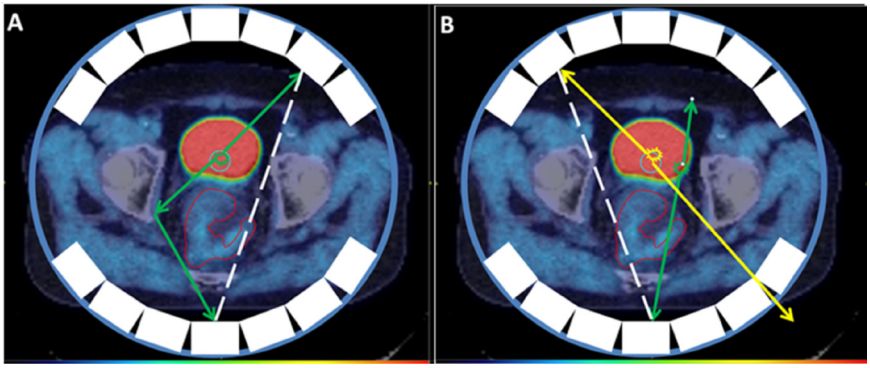

Figure 3: Artwork showing examples of scatter & random events originating from the activity inside the bladder as a potential cause of spill-in counts inside the tumour. The blue circular ring illustrates the PET scanner field of view, the white rectangular blocks represents the photon detectors, green and yellow arrows describe the path of the photons from two different annihilation events, red boundary represents tumour ROI and white dashed line shows the line of response (LOR). (A) An annihilation event occurs in the bladder and the path of a scattered photon is shown using green arrows. The two photons are detected between a pair of opposite detectors in 511 keV energy coincidence window and their LOR (white dashed line) passes through tumour, falsely contributing to the image as a true event. (B) Two annihilation events occur in the bladder and one of the photons in each annihilation gets lost (or undetected) and the other two photons (one from each event) are detected between a pair of opposite detectors in 511 keV energy coincidence window and their LOR (white dashed line) passes through tumour (red boundary), falsely contributing to the image as a true event. PET=positron emission tomography; LOR=line of response; keV=kilo electron volt; ROI=region of interest.

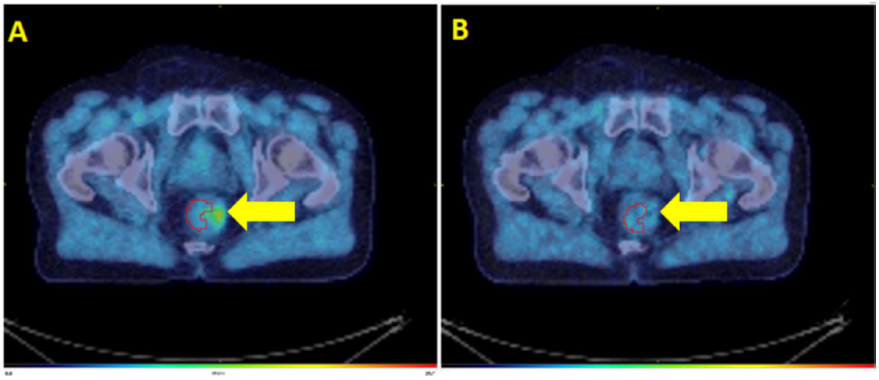

Figure 4: Example from the enema group showing the PET-CT scans at 2h (A) and 4h (B) for the same transaxial slice in the same subject. The red ROI marks the tumour and the yellow arrow shows the non-tumour activity in close proximity to tumour ROI. A and B highlights the fact that the non-tumour [18F]FMISO in the rectum in close proximity to the tumour is visible at 2h, but not after the enema given before the 4h scan. PET=positron emission tomography; CT=computed tomography; ROI=region of interest; [^{18}F]FMISO=[^{18}F]fluoromisonidazole.

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ETHICS, CONSENT AND PERMISSIONS

Informed consent was obtained from all participants included in the study. All involving human participants were in accordance with the local ethical standards and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The research ethics committee (REC) was the East of England – Essex Research Ethics Committee (reference number 13/EE/0123). The Radiotherapy & Imaging Trial Oversight Committee (RIOC) fulfilled the roles of the trial steering committee (TSC) and data and safety monitoring committee (DSMC).

EACR Travel Fellowship – Vicky Forster

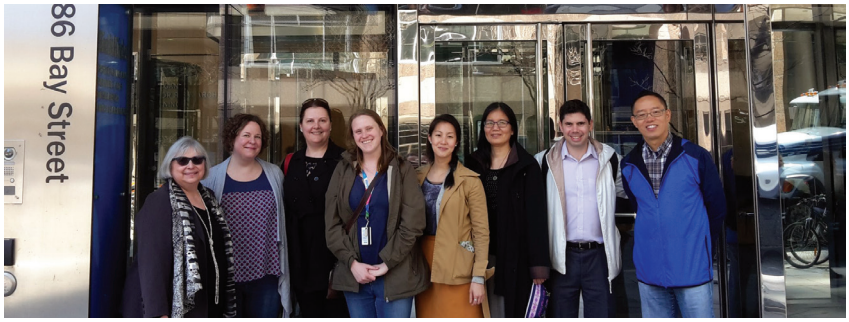
Vicky Forster, an EACR member of nearly 8 years and an EACR ambassador has taken up a postdoctoral position in paediatric brain tumour research in Toronto, Canada after a successful EACR funded trip there last year. In January 2017, Vicky also featured on the Forbes 30 under 30 in Europe list for Science & Healthcare after being selected out of almost 1000 candidates!

I was incredibly lucky to be awarded an EACR Travel Fellowship to do a placement in the lab of Professor Rosanna Weksberg at SickKids in Toronto, Canada. My current postdoctoral work focuses on investigating mechanisms of neurotoxicity in childhood leukaemia patients treated with methotrexate, a common chemotherapy agent. The majority of patients undergo treatment with methotrexate and experience no significant toxicity, but some have severe symptoms such as paralysis and seizures. My work aims to investigate why these patients are so badly affected. The Weksberg lab in Toronto are part of a large, collaborative project which looks at long-term neurocognitive impact of methotrexate on leukaemia survivors, and are currently looking at changes in DNA methylation as a possible causative factor. Given the substantial overlap between our two research areas, we decided to collaborate and use my cell line models to see if there were any changes in global DNA methylation patterns after methotrexate dosing.

I sent my DNA samples ahead of me to be processed on the new methylation array so that the data would be available by the time I arrived in Toronto. When I arrived, my first few days were a fairly intensive crash course in learning to use the relevant software and techniques. For someone who is broadly a lab-based molecular biologist, the thought of spending an entire month doing bioinformatics was somewhat daunting! However I was incredibly lucky to have the support and expertise of members of the Weksberg lab and quickly learned the basics needed to begin analysing my data. I'm pleased to say that the data are excellent and will hopefully lead to a publication in the not-too-distant future. I attended lab meetings with the group and gave two presentations during my time there to get feedback and suggestions on my ongoing project. During my time, I also attended a number of high-quality seminars and presentations given by both external and internal speakers.

I really enjoyed experiencing Toronto as a city too. It's incredibly diverse and I lived in a wonderful neighbourhood with two very hospitable hosts who really made my stay comfortable and easy. I took the opportunity to get involved in various events including a meet up of the Toronto Women in Science and Technology (TWiST) and a half marathon in aid of SickKids which was covered by the local TV station! Doing the training runs was made exceptionally easy by running on the shores of Lake Ontario in the sunshine…and rewarding myself with ice-cream afterwards!

Toronto is an incredibly vibrant and varied place for top-quality medical research at numerous different research institutes, many clustered around a few blocks in the centre of the city. Experiencing this culture and community was invaluable for my professional development. As well as facilitating the valuable collaboration with the Weksberg lab, my visit ultimately led to an offer of a postdoctoral position at SickKids in the Tabori lab working in paediatric brain tumour research, which I began in early 2017. I'd like to thank the EACR once again for funding my Travel Fellowship and supporting me at a very exciting and pivotal stage of my career.



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2017

November

Royal Marsden Pain and Opioid Cancer (2-Day) Conference
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Management skills for oncologists
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18th Annual Meeting of the Society of Urologic Oncology
28 November - 2 December 2017; Washington, DC, USA
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NOA Winter School 2017 "Save the date"
30 November 2017; Bochum, Germany
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December

For Clinical Nurse Specialists - An Update on the Management of Advanced Prostate Cancer
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2nd Global Adolescent and Young Adult (AYA) Cancer Congress
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2018

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February

Treatment advances in Haemato-oncology
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March

Neuro-oncology Conference
8 March 2018; London, UK
E: conferenceteam@rmh.nhs.uk
T: +44 (0)20 7808 2921
W: www.royalmarsden.nhs.uk/studydays
@trmeducation

5th Symposium on Molecular Pathology in Oncology
15 March 2018; London, UK
E: conferenceteam@rmh.nhs.uk
T: +44 (0)20 7808 2921
W: www.royalmarsden.nhs.uk/studydays
@trmeducation

June

International Symposium in Paediatric Neuro-oncology
29 June – 3 July 2018; Denver, USA
W: ISPNO2018.org

Cancer and Bone Society (CABS) 2018 Meeting, jointly with the 8th International Workshop on Advances in the Molecular Pharmacology and Therapeutics of Bone and other Musculoskeletal Diseases
30 June – 3 July 2018; Oxford, UK
W: http://www.molpharmworkshop.org

October

EANO 2018
11-14 October 2018; Stockholm, Sweden
W: www.eano.eu

ESMO 2018 Congress
19-23 October 2018; Munich, Germany
W: esmo.org

November

SIOP 2018 Annual Meeting
16-19 November 2018; Kyoto, Japan
E: siopoffice@kenes.com
W: http://siop-online.org/event/siop-2018

2019

September

EANO 2019
18-22 September 2019; Lyon, France
W: www.eano.eu

Are you organising an annual meeting or conference which you would like to tell our readers about?
Or would you like to write a report on a meeting or conference of particular interest?
If so, contact Denys Wheatley at Oncology News on E: info@biomedes.co.uk

BNOS 2017

Date: 21-23 June 2017. **Venue:** Edinburgh, UK. **Report by:** Maryanne Roach on behalf of the BNOS Council and BNOS 2017 organising committee. The full report is available on the BNOS website at https://www.bnos.org.uk/events/bnos-conference/, as are videos of the keynote speaker presentations.

British Neuro-Oncology Society


Reception

Approximately 250 people with an interest in neuro-oncology attended "Engaging Science, Enhancing Survival" in Edinburgh from 21 to 23 June, 2017. Many papers focused on new insights into the genomic and epigenomic landscape of glioma and the development of animal models to replicate both aspects. More is now understood regarding the mechanism by which transcriptional factors found in glioma drive unconstrained self-renewal of neural stem cells and work is now progressing to investigate whether the Zika virus penetrates and targets glioma stem cells.

As better triage procedures are required to help GPs know whom to refer for urgent imaging, an infrared spectroscopic method based on a serum sample is being developed as a cancer/no cancer test. It takes 10 minutes and appears economically viable – but would a GP feel able to withhold referral after a negative test even though symptoms had justified invoking the test in the first place?

The WHO 2016 biomarker-based classifications appear to be well established and the role of biomarkers in the sub-classification of medulloblastoma is now evident in impact on treatment, most notably the possibility of reducing aggressive treatment in the better prognosis sub-groups to limit long term toxicity.

One might be forgiven for thinking that biomarker assays could now drive all diagnosis and treatment decision-making; however, tumours are notoriously heterogeneous and plastic over time and it is not always possible to obtain the repeated tissue samples required to conduct assays. Hence, while identification of biomarkers is now vital, there is definitely still a role for sophisticated imaging techniques and integrated diagnostic-phenotypic-genotypic methods.

Formal surgical trials are rare. Hence, it was encouraging to hear proposals for two prospective multi-centre trials to compare intra-operative imaging techniques (MRI and ultrasound) and 5-ALA with white light microscopy. It was, however, depressing to hear of the slow uptake of use of 5-ALA across the UK. Surgeons should perhaps be creative in finding savings elsewhere in order to fund its use; for example, in Southampton measures have been introduced to ensure high rates of elective admissions and reduced length of stay, theirs being the lowest in the UK, without compromising readmission, re-operation or mortality rates. This has proved popular with patients, improved efficiency and reduced cost, cancellations and waiting times.

Although awake surgery and intra-operative MRI are effective individual aids in preventing damage to functional brain while maximising the extent of resection, and despite high levels of patient satisfaction, using them together is demanding for the anesthetic and nursing teams and for the patient, at 10 hours the theatre times being about two hours longer than for a standard craniotomy.

We know that residual cancer cells remain at the margin even after gross total resection and that targeting this invasive region is vital in the development of new therapies. There were a number of reports of animal studies with locally delivered chemotherapy and an example which has reached man is that of irinotecan incorporated into biodegradable hydrogel microspheres for injection into the post-surgical cavity wall.

There was discussion of radio-sensitisation in glioma stem cells by poly ADP ribose polymerase (PARP) inhibitors and ataxia–telangiectasia mutated kinase (ATM) inhibitors. A UK consortium is developing a multi-arm/multi-stage trial in collaboration with AstraZeneca to test their portfolio of DNA damage response candidates.

The two proton beam installations being built in the UK will start clinical practice in summer 2018 (Manchester) and 2021 (London). The first priority is to repatriate patients who would otherwise have gone abroad before commissioning more "core" indications (e.g. medulloblastoma) and adding evaluative trials for further indications. Once both centres are fully functional it is anticipated that 1500 patients will be treated per year (1% of current patients treated with photon radiotherapy).

There are still many unanswered questions referring to the management

of low grade gliomas and the long survival times mean that valid surrogate endpoints are required. One also has to consider additional management factors as well as survival advantage, for example the psychological effect of providing patients with an estimate of projected survival possible if biopsy, and hence biomarker assay, has been conducted, or the reduction in seizures resulting from surgery and irradiation even if not associated with radiological or clinical response.

If, as suggested, existence of pre-operative seizures is a significant predictor of post-operative seizures, it may be possible to withhold anti-epileptic drugs in some patients. Whilst seizures are less common in high-grade gliomas, it has been found that secondary, transformational high grade gliomas (as opposed to primary, de novo ones) and the presence of IDH mutation are associated with increased likelihood of seizure at presentation.

Increased survival in childhood cancer poses logistical challenges in follow up and study of the many potentially significant long term side effects. A study is being conducted to see if subsequent restoration of fertility can be effected by preserving tissue and oocytes in pre-pubertal children prior to their treatment.

The vast majority of the increased incidence of brain tumours is due to gliomas occurring in patients over 70 in whom there is poorer prognosis due to more aggressive biology, frailty, co-morbidities, and issues with access to care. It was recommended that up to age 69 the aim should be maximum resection and chemo-radiation, and likewise in older patients who are MGMT promoter positive (or temozolomide alone if they can't tolerate radiotherapy). There was a call for a new study of chemo-radiation versus temozolomide alone after gross resection in MGMT promoter positive patients over age 70.

In answer to the considerable interest shown in diet, two parallel multi-centre open-label Phase II randomised trials of the Modified Ketogenic Diet are due to open in patients with high and low grade gliomas. Many factors have had to be taken into consideration during trial design, including how to ensure that patients accept randomisation and do not self "prescribe", and the amount of dietetic support available.

Results are awaited for two trials of dendritic cell vaccines in glioma and the REO-Glio trial - which adds reovirus, an oncolytic virus, and GM-CSF pre-treatment to standard of care chemo-radiation in adult glioma - will open summer 2017.

Current methods of drug discovery via genomics and identification of molecular targets are proving of no real success, whilst being very long and costly, and hence phenotypic screening via high throughput microscopy and stem cell technology, with target deconvolution only at a late stage, is now being tested.

International collaboration has been highly effective in conducting trials in medulloblastoma but unfortunately the picture is not the same in adult brain tumours. Recruitment is challenging, barriers being mainly ones of resources, differing patient pathways, and lack of trials. In order to recruit all brain tumour patients in the UK, all centres should take part in trials whereas currently many feel that the set up effort is not worthwhile if they are only likely to have a handful of appropriate patients.

A rather different topic listed all the different types of biases that can affect physician and surgeon decision-making and the advice they give to patients. Attendees were also introduced to the role of qualitative research via semi-structured, face-to-face interviews.

Appendix

Young Investigator of the Year Award, jointly funded by BNOS and Brain Tumour Research: Harry Bulstrode, University of Cambridge:

Best poster prize: "18F-methylcholine PET/CT, in vivo magnetic resonance spectroscopy imaging and tissue enzyme biomarkers of choline metabolism in primary brain gliomas": Matthew Grech-Sollars (Imperial College, London)

Best scientific oral presentation: "A human iPS cell-based model of medulloblastoma demonstrates cooperativity between SHH signalling and mutation in an epigenetic modifier": Jignesh Tailor (St George's University Hospital, London)

Best clinical oral presentation: "The impact of visual impairment on Health-Related Quality of Life scores in brain tumour patients": Sana Sharrack (University of Cambridge)

BNOS 2018 will be held from 4-6 July in Winchester

European Association for the Study of the Liver (EASL) International Liver Congress™

Date: 19-23 April 2017. **Venue:** Amsterdam, The Netherlands.

SIRT opens new door for advanced HCC

Advanced or inoperable Hepatocellular Carcinoma (HCC) patients randomised to liver directed Selective Internal Radiation Therapy (SIRT) showed similar overall survival (OS) to patients randomised to standard of care sorafenib, as reported from the phase 3 French SARAH study. Although the trial failed to meet its primary endpoint, the investigator-led study showed patients receiving SIRT had statistically fewer adverse effects and better quality of life.

"SIRT offers a better tolerance with less treatment-related adverse events and a better quality of life than sorafenib. We think this is very important when patients suffer from a severe disease with a poor life expectancy," said Professor Valérie Vilgrain (pictured), the PI from Hôpital Beaujon Service de Radiologie, Paris. The results, she added, have opened a new door in the field of HCC.

SIRT is a form of internal radiation therapy involving Y-90 resin microspheres (diameter 20-60 microns), delivered through a catheter to the hepatic artery. The β-radiation emitting microspheres lodge preferentially in the microvasculature surrounding tumours, minimising systemic effects.

Between December 2011 and February 2015, 459 patients with locally advanced HCC and patients with non-resectable tumours who had failed transarterial chemoembolisation (TACE) from 25 centres across France, were randomised 1:1 to SIRT (n=237) or sorafenib (n=222, 800mg daily).

Results for the intention-to-treat (ITT) population show the median OS was 8.0 months for SIRT versus 9.9 months for sorafenib (p=0.18), whereas for those actually receiving treatment (SIRT n=174; sorafenib n=206) OS was 9.9 months for SIRT versus 9.9 months for sorafenib (p=0.92).

The study showed significantly fewer SIRT patients had any treatment related side effects (76.5% for SIRT versus 94.0% for sorafenib; p<0.001), and that they were less severe (≥grade 3, 40.7%

for SIRT versus 63.0% for sorafenib, p<0.001). Quality of life (EORTC QLQ-C30 questionnaire) showed SIRT patients reported significantly better quality of life (P=0.005).

Objective response (complete response and partial response, measured with RECIST v 1.1) was 19.0% for patients treated with SIRT versus 11.6% for patients treated with sorafenib (p=0.042). Although the numbers were small, Professor Vilgrain said that more SIRT patients were able to access curative treatments, and also added that they will evaluate prognostic factors for SIRT, cost effectiveness and dose related efficacy.

Reference

Vilgrain V, Bouattour M, Sibert A, et al. SARAH: a randomized controlled trial comparing efficacy and safety of selective internal radiation therapy (with ytrrium-90 microspheres) and sorafenib in patients with locally advanced hepatocellular carcinoma. Abstract GS-012.

Nivolumab delivers durable responses for sorafenib experienced HCC

Nivolumab had durable responses with long-term survival in sorafenib-experienced advanced HCC patients, regardless of Hepatitis B or C infections, according to the CheckMate 040 study reported at the conference.

Currently the multi-kinase inhibitor, sorafenib, is the only approved systemic treatment for advanced liver cancer. Nivolumab, a programmed-death immune checkpoint inhibitor – already used in kidney, melanoma and non-small cell blood cancer – is not yet licensed in the EU for HCC.

For the phase 1/2 study, 262 HCC patients who had previously been treated with the sorafenib and who were not eligible for surgical resection, were given iv nivolumab 3mg/kg every two weeks. Altogether, 132 (91.0%) patients had progressed on sorafenib and 12 (8.3%) were intolerant. The Spanish investigators were presenting results for a cohort of 145 patients (HCV, n=30; HBV, n=43; uninfected, n=72). Their findings showed the objective response rate (using RECIST v1.1 by blinded independent central review) was 14.5% (HCV 20.0%; HBV 14% and uninfected 12.5%). The median duration of response (DOR) had not been reached, and 8/21 responders had a DOR of > 12 months. Median overall survival was 16.7 months. Overall, grade 3/4 treatment-related adverse events occurred in 16.6% of the patients (HCV, 30%; HBV 9.3%; uninfected 15.3%), with the most frequent adverse effects being fatigue (24%), itching (19%), rash (16%) and diarrhea (14%).

"These results suggest nivolumab is a valuable option in the treatment of patients with HCC who progress on or are intolerant of sorafenib," said Professor Bruno Sangro, Clinica Universidad de Navarra, Pamplona.

Professor Alejandro Forner, a member of the EASL governing body from the Hospital Clinic Barcelona, commented, "The reported median survival of 16.7 months in patients previously treated with sorafenib is promising and it encourages the evaluation of nivolumab in patients affected with hepatocellular carcinoma."

CheckMate 459, a randomized phase 3 study is now underway comparing nivolumab with sorafenib in first-line treatment of patients with advanced HCC.

Reference

Sangro B, Yau T, Hsu C, et al. Nivolumab in sorafenib-experienced patients with advanced hepatocellular carcinoma (HCC) with or without chronic viral hepatitis: CheckMate 040 study. Abstract GS-010.