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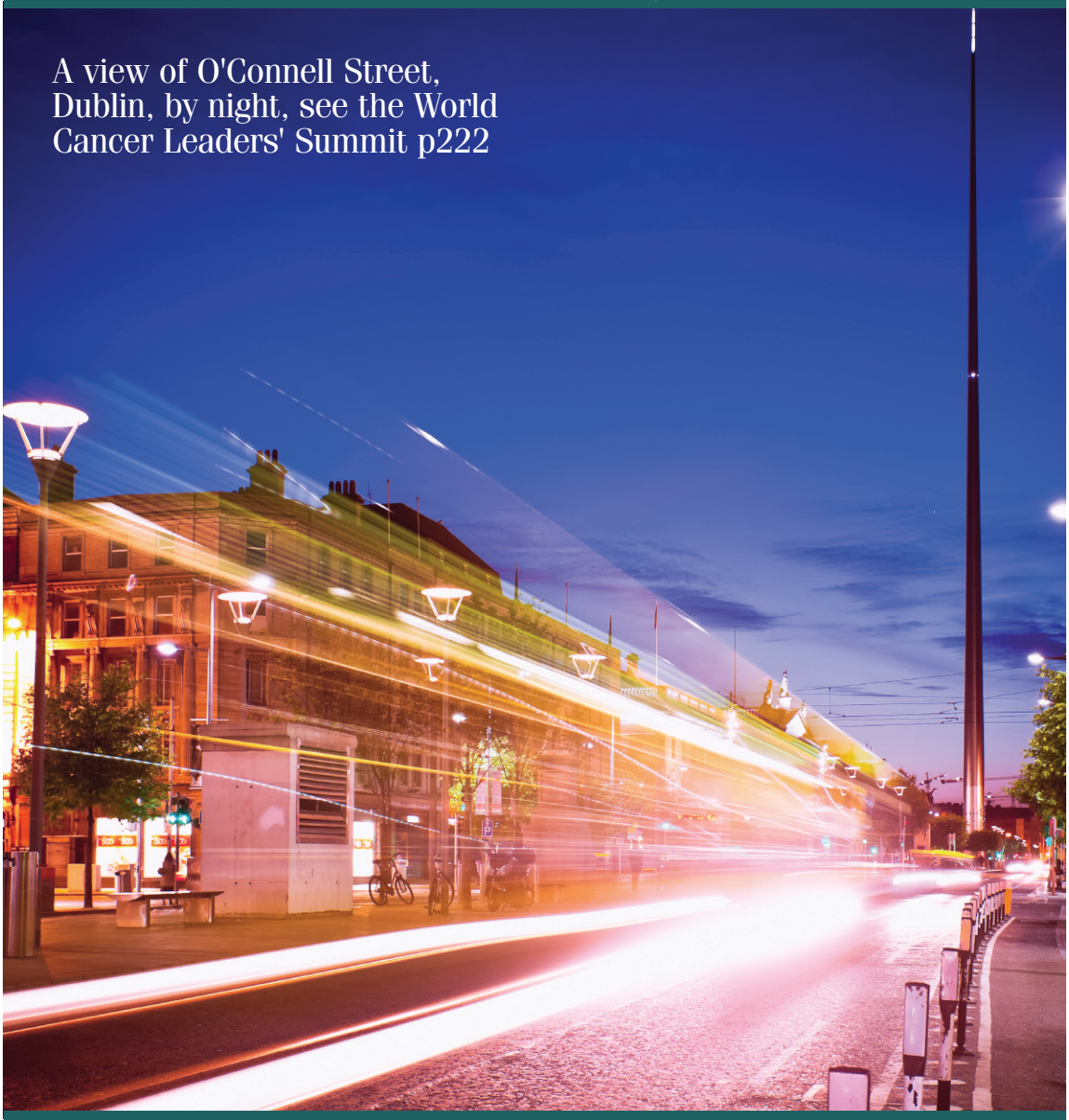

A view of O'Connell Street, Dublin, by night, see the World Cancer Leaders' Summit p222

In this Issue

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Mobile phones: another example of radiation carcinogenesis?

Denys Wheatley, Editor.

There is considerable controversy over the damaging effects of mobile phones on human health, especially in young people who happen to be amongst the heaviest users of them, the very people who will probably continue to be exposed to them for the rest of their long lives. These conditions could lead to accumulation of damage that cause disorders of the brain (mind) and body. The International Agency for Research on Cancer (IARC) considers the radiation from mobile phones to be possibly carcinogenic, classifying the risk as Group 2B [1]. An analysis of the risk in different age categories, based on the first use of a mobile showed that it was highest in young people, i.e. those of < 20 years of age [2]. This could be associated with the fact that more energy of RF-EMF waves are absorbed by brain tissue in young persons due to their thinner cranial bones than adults.

In the CEFALO report from a multi-centre case-control study (from three Scandinavian countries and Switzerland) that has recently been published [3], the conclusion was reached that mobile phones do not appear to be harmful – "*showed no increased risk of brain tumours*" [3]. However, to be more accurate, there was an increased incidence of tumours in regular mobile phone users, but the difference was not found to be statistically significant from the controls that had been used. The data on which this conclusion was based has now been challenged by another research group, who believe the evidence presented in CEFALO is insufficiently sound [4], and who argue that radiation from mobile phones is harmful, in accord with the findings in other reports, mainly on adults [e.g. 5-6].

Apart from other disorders that might be due to RF-EMF that will not be dealt with in this editorial, Söderqvist and his colleagues claim that the relative risk of gliomas in young users of mobile phones is at least twice that found in control subjects, which is difficult to imagine can be insignificant, especially as other reports indicate a similar level of risk. Brain tumours and acoustic neuromas are found in subjects who have used mobile phones extensively over the last decade, with lesions more often on the side of the head that the phone was held [5]. The question has also been raised as to what constitutes a mobile phone, i.e. whether or not to include cordless phones of the DECT type. If use of these are included as part of the 'unexposed' group, any difference in tumour risk might appear less obvious (significant) [3]. Not only were "first use" subjects under 20 years at the greatest risk, by the incidence gauged at diagnosis was also highest in the youngest age group. The report from CEFALO has also been criticised as being based on a less than adequate sampling, and a relatively short-term of observation (five years), which would not impact on low-grade astrocytomas seen in youngsters compared with older subjects. Development of low-grade astrocytomas (predominant in the young) into the high-grade category (predominant in adults) is not going to happen in the short term. Clearly any damage caused by radiation energy will have a cumulative effect with prolonged use of mobile phones, which depends not only on how often the phones are used, but on the *length* of the calls made on them.

Since, it is unclear how RF-EMF exposure might cause or promote cancer, it is difficult to find hypotheses that could help direct research towards finding more accurate ways of assessing the potential risk. If there is indeed a causal relationship between exposure and cancer, any idea of what might be considered a safe threshold is seen as premature [3].

But a number of things are more certain: (i) mobile phones are here to stay, for the foreseeable future, (ii) as many as five billion people may currently be using them, (iii) many people using mobiles will live for considerably longer than people of past generations as longevity increases, allowing more time for lesions to progress, and (iv) dogma has it that no level of radiation is without risk (which can also apply to RF-EMF*), and therefore the only absolutely "safe" threshold is zero exposure. With these considerations in mind, the dilemma is how to make these machines as safe as possible, other than devising some new harmless technology to replace them. Prompt action is needed in this regard, as it is unlikely that we will learn how RF-EMF induces cancers any sooner than we will find an alternative technology.

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* There are scientists in the field that consider non-ionising radiation to be perfectly safe as long as its intensity does not cause heating effects, which mobile and DECT do not. Hence, the main question is whether non-ionising non-thermal (low-intensive) RF-EMF is carcinogenic.

Awards & Appointments

Scientist recognised with Cancer Charity's Highest Honour

Professor Mel Greaves from The Institute of Cancer Research (ICR) has become the first scientist honoured with a leading blood cancer charity's highest award.

Leukaemia & Lymphoma Research selected Professor Greaves to receive a lifetime achievement award (Certificate of Merit) in recognition of his "outstanding service" to the charity.

The charity's trustees singled out Professor Greaves' internationally renowned research into the origins of childhood leukaemia, and in particular his pioneering studies in twins that deciphered the sequence, timing and complexity of genetic mutations in childhood leukaemia.

"I am delighted and honoured that my team's research over many years at The Institute of Cancer Research has been recognised in this way. It has been very rewarding and exciting to have been part of the worldwide effort that has changed the landscape of both the biology and treatment of childhood leukaemia," Professor Greaves says.

"There is still work to be done: a minority of children still fare badly and the treatment, albeit usually successful, can carry considerable side-effects. We have evidence that the development of ALL in susceptible individuals is trigged by infection. If we could establish this unambiguously, then

prevention, perhaps by vaccination in infancy, could become an achievable objective."

Professor Greaves discovered that pre-cancerous stem cells can arise from an abnormal fusion of two genes – TEL (ETV6) and AML1 (RUNX1) – in the developing foetus during the mother's pregnancy.

The pre-leukaemic stem cells grow in the bone marrow as a silent time bomb that can stay in the body for up to 15 years, but require other triggers and genetic events to convert into the most common form of childhood cancer, acute lymphoblastic leukaemia (ALL).

Evidence suggests that the initial mutation may be present in as many as one in 100 newborns, but only about one in 100 of those children with the mutation then go on to develop leukaemia.

His team also established that these cancer stem cells continue to evolve in a Darwinian fashion by ongoing genetic variation and natural selection. The mutational complexity of the stem cells driving the disease helps explain why advanced cancers are notoriously resistant to treatment.

Professor Greaves' later work has shed further light on the events necessary for leukaemia to evolve into malignant disease, including the involvement of a molecule called TGF. TGF is released in the body as a normal response to infection, so the finding also provided the first experimental evidence – endorsing the team's epidemiological observations – that common childhood infection may be critically involved in triggering the clinical emergence of leukaemia.

Professor Greaves received the award at Leukaemia & Lymphoma Research's Annual Grantholders' Day on November 9 2011. ■

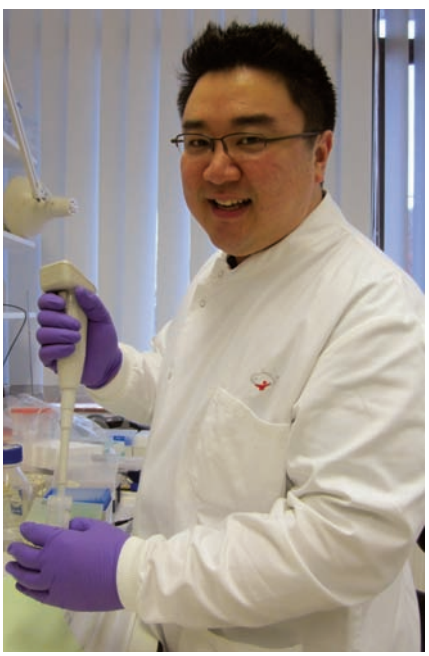
Global award for prostate cancer blood test developer

A scientist at The Institute of Cancer Research (ICR) and The Royal Marsden NHS Foundation Trust, Dr Timothy Yap, has received an award for ongoing work developing a blood test to predict how prostate cancer patients will respond to treatment.

The Prostate Cancer Foundation's Young Investigator awards are designed to encourage the most innovative minds in cancer research to focus their careers on prostate cancer. Each Young Investigator receives $225,000 over three years to help support their research focussed on prostate cancer treatment and patients.

In collaboration with his mentor Professor Johann de Bono, Dr Yap is studying Circulating Tumour Cells (CTCs), cancer cells that have broken away from an existing tumour and entered the blood stream.

The team's previous work has suggested



that doctors could monitor how well patients are responding to new drugs by measuring the levels and molecular characteristics of CTCs in their blood. Currently, to assess whether a drug is working doctors must rely on techniques such as imaging or biopsy, which are slow to show results and may lead to other complications, or PSA testing, which has questionable accuracy.

"This blood test could be used to confirm that the drug is benefiting a particular patient; and, if not, they can be moved quickly to an alternative therapy," Dr Yap says. "This would also mean they suffer fewer side-effects from unnecessary treatments and expensive new drugs are not given to patients they cannot help. I am grateful and honoured to have received this prestigious award, which will enable us to assess this test in a large-scale clinical trial." ■

PRIMe Awards 2011

Novartis Oncology is pleased to announce the winners of its 2011 Promising Renal Investigators Meeting (PRIMe) Awards following a two day meeting held in London. These prestigious awards, in their second year, see researchers from the UK and France presenting their research projects to a panel of eminent experts and are designed to showcase and reward the efforts of emerging investigators and research teams helping to advance science in the fight against kidney cancer.

Dr Chiara Margiotta (pictured top), based between the School of Cancer Science of the University of Birmingham and the Cancer Centre of the Queen Elizabeth Hospital in Birmingham, was recognised for her research programme, and will receive a €10,000 grant to support its completion.

Dr Margiotta is conducting a translational research initiative in which blood and tissue samples from patients receiving tyrosine kinase inhibitors (TKIs) are subjected to phosphoproteomic profiling, in order to assess the mechanisms of the TKIs efficacy and toxicity and potentially identify new clinical targets. TKIs are drugs that interfere with cell communication and growth and may prevent tumour growth [1].

Commenting on her work and the win Dr Margiotta said, "I'm truly honoured to have won this award which will allow for continued laboratory work to further our understanding of TKI mechanisms and targets, offering further hope for the future treatment of this disease".

Dr Elodie Coquan (pictured bottom) of the Centre de Lutte Contre le Cancer François Baclesse, Caen was the French prize winner and was recognised for an innovative pilot study to correlate pharmacokinetic parameters and safety and efficacy endpoints of everolimus in the treatment of advanced renal cell carcinoma. ■

PRIMe
PROMISING RENAL INVESTIGATORS MeeTING
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Reference

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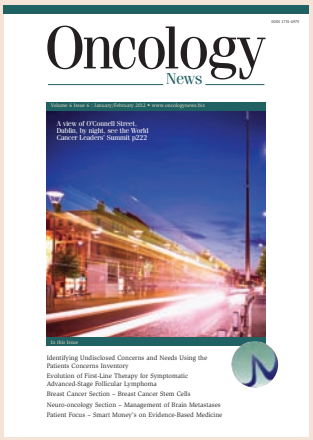

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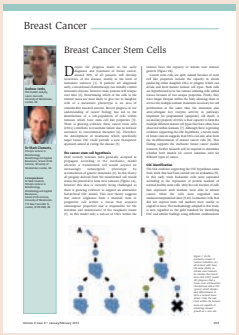

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Identifying Undisclosed Concerns and Needs Using the Patients Concerns Inventory (PCI):

A Model of Care Suitable for Routine Use in Busy Oncology Clinics as Piloted and Modeled in Head and Neck Cancer

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Cancer survivorship is a matter that is becoming increasingly important [1]. The assimilation of novel therapeutic developments into the standard of care in many cases has successfully transformed the course of cancer into a chronic disease, where long-term survival is now expected. Previously, the emphasis on 'survival' meant that cancer services focused centrally on issues of diagnosis, staging and treatment [2,3]. Oncology teams strove to provide optimal treatment to ensure patients get through to the end of treatment successfully to facilitate a return to 'normality'. The follow-up period after treatment has been viewed as a time of 'watchful waiting', where resources were concentrated on diagnosing potential recurrence or new primary lesions [4]. From this perspective, some have questioned the value of long-term follow-up [5] and suggest five-year surveillance was 'adequate' [6]. There was a general lack of appreciation among cancer networks of the long-term effects of treatment and other far-reaching fall-outs of cancer that continue to impact upon those who survive or are living with cancer. The holistic experience of the journey through this phase is often regarded as 'cancer survivorship' [7].

The paradigm shift from 'survival' towards 'cancer survivorship' is borne from the success story of "curative" treatment in many cancer types. The central focus of cancer survivorship is on recovery, well-being and health following treatment [7]. Cancer networks are now asked to shift their emphasis towards managing potential issues stemming from the original treatment, which are often protracted in nature. Indeed, a heavy price is incurred with "cure", not only on the physical well-being of survivors from the side effects of treatment, but also in many other facets of their lives. The cancer survivor is forever changed by their diagnosis and treatment. The post-treatment phase is a difficult time psychosocially, as patients gradually adjust to 'life after cancer' [8]. Dealing with uncertainty refers not only to the possibility of the cancer returning and the threat to life that it brings, but also includes the uncertainties relating to employment and financial security. Changes to the dynamics of interpersonal relationships at home and work occur as a result of the patient's personal transformation from their experience of cancer. The diversity of issues experienced by individual patients and their carers during their cancer journey can generate various needs for supportive care. This highlights another element of the paradigm shift that occurs with cancer survivorship, which is the move away from 'one size fits all' approach to patient care to a 'personalised' model of care planning, where individual risks, needs and preferences form the basis of patient-centred care [7]. Shared decision-making is central to this process. This is particularly crucial in the cancer survivorship setting, where the individual needs of patients and their carers can require specialist input from multidisciplinary professionals at different stages [9].

Head and neck cancer (HNC) is a good model in which to develop and evaluate a suitable tool for shared decision-making during the survivorship period as the management of this group of patients is known to be resource intensive and multidisciplinary [2]. Head and neck cancer refers to malignancies arising from the lip, oral cavity, oropharynx, nasopharynx, larynx, nasal and paranasal sinuses. Over the last three decades, improvements in HNC management have resulted in better treatment outcomes in the UK [10], some parts of Europe [11] and North America [12,13]. With increased survival, many more HNC patients experience long-term survivorship, where they and their caregivers encounter a whole range of issues, concerns and needs at different times during their cancer journey based on the diagnosis and treatment received.

Head and neck cancer patients who have undergone surgery and/or multimodality therapy can experience significant morbidity from debilitating functional deficits and facial disfigurement. Survivors of HNC also suffer from substantial symptom burdens [14]. Psychological distress is prevalent in this cohort [14], often causing depression [15-17], anxiety [16-19], and mood disorders [17]. Recurrence is feared by many survivors [15], but is frequently undisclosed. Some experience other worries, such as employment [20,21] and financial problems [21]. Caregivers often shoulder the load of the care-giving burden [18,19], and also experience psychological distress [23]. These problems may be compounded by pre-diagnosis states, such as deprivation [24], substance addiction [15] and medical comorbidities. The process of self-acceptance of the cancer diagnosis and adaptation to the consequence of treatment requires supportive care over time and the patients can experience high levels of unsatisfied needs across various aspects of life [25,26]. Indeed, serious psychological distress and issues relating to disfigurement in HNC patients often go unrecognised and unmet [18,27,28].

It can be difficult to identify the patient who 'suffers in silence'; many take a stoical view and are unwilling to disclose worries or complain. Some are reticent in discussing sensitive and embarrassing issues like intimacy [29]. Others with lowered self-esteem [30] who find the clinical setting intimidating may feel unable to voice their concerns, despite regularly attending sessions as part of their cancer surveillance programme. The outpatient clinic setting can be busy, frenetic and demanding for both the patient and clinician. Patients may be anxious, unwell and experience long waiting times before being seen. In addition, clinicians are under pressure to perform cancer surveillance tasks, examine prosthesis/wounds and provide information, advice and reassurances during this small window of opportunity. Thus, some issues regarding patient concerns may be missed completely [19] and others are

superficially addressed due to a combination of time and logistical constraint [28], patient's reticence and, perhaps, the clinician's unwillingness to broach challenging and sensitive issues in which they may feel inadequately skilled or trained.

Other barriers in assessing patient needs exist, in particular, the absence of best practices in identifying needs [31]. In a recent survey of nurses involved with HNC patients, over three-quarters felt strongly about their personal role in uncovering unmet needs in patients [32]. They had tended to use counseling and communication methods to identify patients concerns rather than screening tools, such as needs assessment questionnaires. Therefore, the extent to which needs and concerns are identified depends largely on the quality of that 'one-to-one' contact, which may not be reliable and consistent across the board. Patients with inadequately addressed concerns and/or unrecognised issues will fail to get the multidisciplinary support they need. The undercurrents of unmet needs can lead to poorer overall health, inefficient use of healthcare [33] and dissatisfaction [26], despite being cancer-free. In these circumstances, there is benefit in introducing a framework-based approach to ensure that the needs might be identified in a standardised manner.

The Head and Neck Patient Concerns Inventory (PCI) was introduced as a site-specific needs assessment tool for use in the outpatient setting [34]. It was developed together with the Merseyside Region HNC support group and is designed to be a holistic, patient-reported instrument that tries to highlight patient's needs and concerns that they wish to discuss during the outpatient clinic. The PCI is a list of 55 items of concerns (Figure 1), ranging from problems of dysfunction to psychosocial issues regarding the HNC and its treatment. Also, the PCI allows patients to choose individuals they wish to see or be referred to from a range of 15 professionals, including those from HNC multidisciplinary teams to other non-medical professionals, e.g. financial advisors and chaplains. By utilising the PCI, patients can take charge of their health concerns and needs.

The PCI is administered along with the University of Washington Quality of Life version 4 (UWQOL) [35] using touch-screen technology [36]. The completion time of the PCI and UWQOL averages eight minutes [35]. The computer summarises the PCI and UWQOL scores per patient immediately upon completion, allowing the information to be used during clinic consultation. The summarised PCI data sheet can also be printed and attached to the customary clinic letter to the general practitioner, facilitating the continuity of oncology care into the primary setting. While the PCI can be paper form, the computerised touch-screen technology is advantageous because it permits self-completion of both questionnaires, provides a permanent record

Figure 1: The Patient Concerns Inventory
THE HEAD AND NECK PATIENT CONCERNS INVENTORY

Please choose from the list of issues you would specifically like to talk about in the consultation/whilst at clinic today. You can choose more than one option: (Tick the box ☑)

❑ Activity	❑ Nausea
❑ Anger	❑ Pain in head and neck
❑ Anxiety	❑ Pain elsewhere
❑ Appearance	❑ PEG tube
❑ Appetite	❑ Recreation
❑ Bowel habit (diarrhoea or constipation)	❑ Regret about treatment
❑ Breathing	❑ Relationships
❑ Carer	❑ Salivation
❑ Chewing/eating	❑ Sex
❑ Dental health/teeth	❑ Shoulder
❑ Depression	❑ Sleeping
❑ Energy levels	❑ Smell
❑ Fatigue/tiredness	❑ Speech/voice/being understood
❑ Fear of the cancer coming back	❑ Spiritual /religious aspects
❑ Financial / benefits	❑ Support for my family
❑ Hearing	❑ Swallowing
❑ Home care/district nurse support	❑ Swelling
❑ Intimacy	❑ Taste
❑ Lifestyle issues (smoking/alcohol)	❑ Temperament and personality
❑ Memory	❑ Vomiting/sickness
❑ Mobility	❑ Weight
❑ Mood	❑ Wound healing
❑ Mouth opening	❑ Anything else

Please indicate the people you would specifically like to talk with either in clinic or by referral. You can indicate more than one person. (Tick the box ☑)

❑ Chaplain	❑ Family doctor	❑ Radiotherapist/oncologist
❑ Clinical nurse specialist	❑ Nursing staff	❑ Social worker
❑ Dental hygienist	❑ Occupational therapist	❑ Speech and language therapist
❑ Dentist	❑ Oral rehabilitation team	❑ Surgeon
❑ Dietician	❑ Physiotherapist	❑ Anyone else

that can be included in electronic case notes, and can aid in service evaluation and audits. The sequence of a PCI-UWQOL directed clinic visit is summarised in Figure 2.

In the cohort of predominantly oral cancer patients in the post-treatment phase, the five most common concerns highlighted by patients on PCI were the fear of recurrence (37%), dental health (27%), chewing and eating (24%), pain in the head and neck region (20%) and fatigue (19%) [34]. Without a tool like the PCI, concerns and fears relating to recurrences are seldom brought into consultation, despite this issue being the main concern for many patients. The need to address the fear of recurrence in those who wish to discuss it is fundamental to alleviating some of the burden experienced by cancer patients [37] and their carers [38]. Compared with a symptom-type concern, for example, difficulties with chewing or tiredness, it is far more difficult to broach a sensitive subject like fear of recurrence without a clear prompt. Furthermore, there are no specific clinical characteristics that can predict those experiencing fear of recurrence to allow effective screening for this problem in the outpatient setting [39]. Worryingly, some patients experience significant levels of fear of recurrence that interfere with their daily life [40], and there is evidence that this fear does not diminish with time [41].

Apart from identifying potential unmet needs, the PCI can encourage effective communication during in clinic consultations. Patients have commented that the PCI 'reminds them of points they want discussed' at the clinic [34]. By generating these prompts, the PCI enables better patient-clinician communication by focusing and personalising their consultation to the specific issues they have highlighted. Information gathering and provision is more efficient. The PCI-directed consultation gives the clinician/

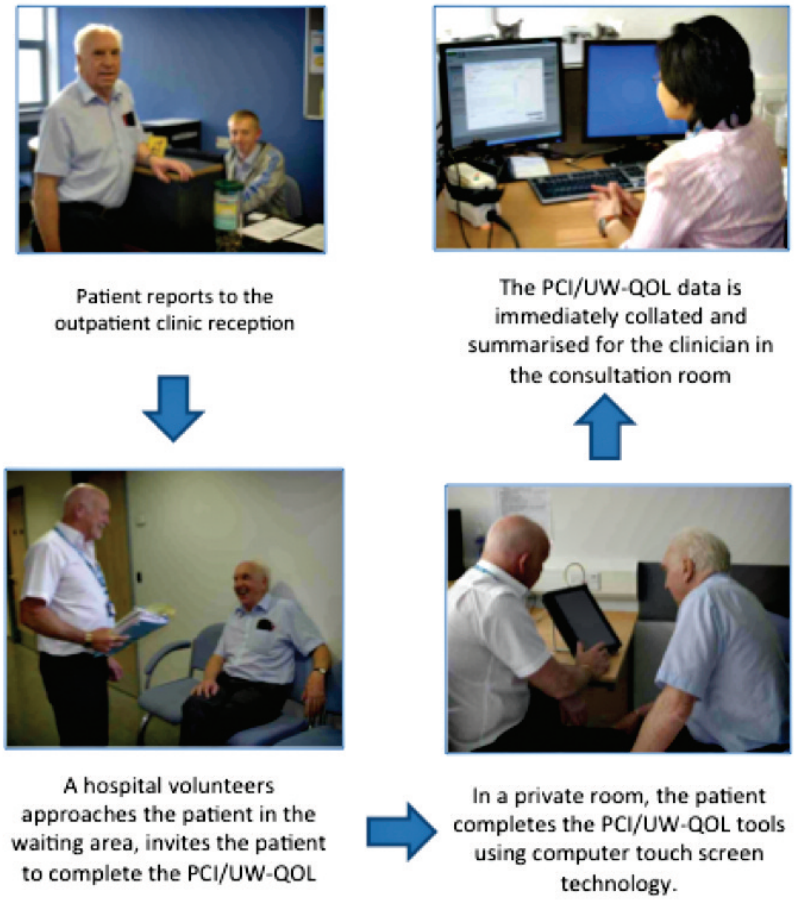

Figure 2: Flow-chart of the PCI/UWQOL-directed clinic consultation

multidisciplinary team a better understanding of the individual patient's concerns and needs, and can apportion the appropriate type and level of healthcare and supportive interventions required.

We have found that with the introduction of PCI in clinic, the referral numbers have not changed, despite routine screening for unmet needs [42]. This indicates that most of the concerns highlighted by patients have been dealt with immediately during a multidisciplinary HNC clinic consultation. Nevertheless, a proportional increase of referrals for psychological support and oral rehabilitation services was observed. This suggests that those with higher and specific needs were reliably identified by PCI to allow for the appropriate dispensation of supportive care.

With the recent emphasis on cancer survivorship [7], holistic needs assessment has taken centre-stage [43] and is predicted to become, like health-related quality of life, a secondary measure of outcome of cancer treatment [44]. There are several needs assessment tools used in oncology [43], but the PCI has a unique role because its simplicity allows for rapid screening and self-identification of issues that can guide consultations. With routine completion of the PCI during the survivorship period, a record of their individual concerns is formulated with time. From the perspectives of the healthcare service, the PCI promotes a multidisciplinary approach in the clinic, where consultation is more likely to take place because concerns and requests for certain professionals are identified before the consultation takes place.

The PCI on touch-screen technology has recently been received the 'Best Use of IT in Patient and Citizen Involvement in Healthcare' award at the national 'E-Health Insider' awards 2010 [45] in recognition of its role in providing a systematic basis to guide out-patient consultations and promote multidisciplinary care. Application of the PCI concept as a tool for shared-decision making in other cancer types such as breast cancer is now being developed alongside its applications in other chronic diseases, e.g. in rheumatology and neurosurgery. Other developments related to the PCI include an evaluation of its roll-out in multiple head and neck oncology clinic settings, and the development of the PCI as an information resource to educate patients on the potential long-term problems following treatment and to support self-management. Further information on the PCI can be obtained from http://www.headandneckcancer.co.uk. ■

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Meet the Editorial Team

Professor Denys Wheatley is Editor, and is Director of BioMedES. He has strong research ties in Albany, Davis, Auckland, Valencia, Detroit, Budapest, St Petersburg, Heidelberg, Zürich and Hong Kong. He is eager to establish strong interaction with cancer and cell biology teams worldwide, and initiate programmes in the areas in which his expertise lies. His work in cancer research, other scientific fields, with IFCB, and in publishing and scientific communication has led to his receiving awards in recent years.

Dr Richard J Ablin (Associate Editor), is Research Professor of Immunobiology and Pathology, University of Arizona College of Medicine and a Member of the Arizona Cancer Center, Tucson, Arizona. He received the First Award for scientific excellence from The Haakon Ragde Foundation for Advanced Cancer Studies. Dr Ablin discovered prostate-specific antigen (PSA) in 1970. A pioneer of cryosurgery and cryoimmunotherapy, he has extensive experience in cancer research.

Alan Cooper is Assistant Editor – Urology, and is Lead Scientist with the urology research group in Southampton University Hospitals and senior lecturer (albeit with virtually no lecturing burden) in the Department of Biomedical Sciences at Portsmouth University.

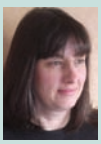
Dr Tom Lynch is Assistant Editor – Imaging, and is a Radiologist and Lead Nuclear Medicine Physician in the Northern Ireland Cancer Centre based at the Belfast City Hospital. Tom specialises in PET/CT scanning and nuclear medicine with a special interest in paediatric nuclear medicine.

Marilena Loizidou is Assistant Editor – Colorectal, and is a Non-Clinical Senior Lecturer in the Department of Surgery, UCL. Her research program focuses on aspects of colorectal cancer and liver metastases, from the basic underlying biology to new potential treatments. The current focus of research is the contribution of the peptide endothelin-1 to tumour growth and progression in the bowel. Additional research areas include breast and bladder cancer.

Dr Miriam Dwek is Assistant Co-Editor - Breast Cancer, she is a Senior Lecturer in Biochemistry at the Department of Molecular and Applied Biosciences, School of Life Sciences, University of Westminster in London.

Mo Keshtgar is Assistant Co-Editor - Breast Cancer, and is a Consultant Surgical Oncologist at the Department of Surgery, Royal Free Hospital, London. His main area of interest is minimally invasive approaches in diagnosis and treatment of breast cancer. His research interest is in sentinel node biopsy, intra-operative radiotherapy, quantum dot nanotechnology in breast cancer.

Willie Stewart is Assistant Editor – Neuro-Oncology, he is a Consultant and Lead Neuropathologist based at the Institute of Neurological Sciences, Glasgow and Honorary Clinical Senior Lecturer in the University of Glasgow. His interests include the pathology of high-grade gliomas and developing molecular diagnostic techniques for introduction to routine clinical practice.



Ms Kathleen Mais is Assistant Editor – Nursing, and is a Nurse Clinician in Head & Neck Oncology at Christie Hospital, Manchester. Kathleen qualified as a nurse in Newcastle-upon-Tyne. Kathleen is a nurse-prescriber and runs a nurse-led chemotherapy clinic as well as continuing her work in clinical research.

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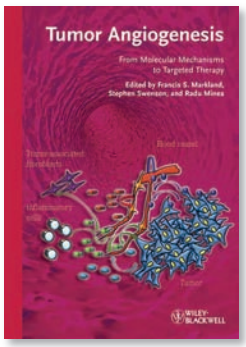
Richard Novell, MChir FRCS, Consultant Coloproctologist, The Royal Free Hospital, London, UK.

Book Reviews

Tumor Angiogenesis: from molecular mechanisms to targeted therapy

Edited by: FS Markland, S Swenson and R Minea. Published by: Wiley. ISBN: 978-3-527-32091-2. Price: £110.00.



This is a specialist text, covering important research topics in cancer biology. It is an ideal reference for oncologists, cell biologists, pharmaceutical chemists, pathologist, molecular biologists and researchers working in the pharmaceutical industry.

Part I: The introduction looks at tumour angiogenesis; Its history and its importance in thrombosis and malignancy. It shows how angiogenesis represents an essential mechanism connecting thrombosis and malignancy and offering new targets for combined therapies.

Part II: mechanisms of angiogenesis and lymphangiogenesis. In particular, it explores molecular mechanisms of angiogenesis, proangiogenic factors, the role of accessory cells in tumour angiogenesis and tumour lymphangiogenesis.

Part III: considers signal transduction and angiogenesis, in particular integrin involvement in angiogenesis and signal pathways in tumour angiogenesis. Five major signalling systems that are involved in tumour angiogenesis are summarised here.

Part IV: Therapeutic approaches and angiogenesis. This section covers development of an integrin-targeted antiangiogenic agent, Anti-VEGF approaches, and newer antiangogenic approaches already in clinical use. Chapter 10; Anti-VEGF approaches, describes the discovery of VEGF and anti-VEGF cancer therapeutics; monoclonal antibodies. It details the discovery and development of Bevacizaumab, describes the clinical trials and its uses in treatment of metastatic colorectal cancer.

Part V: Imaging and biomarkers in angiogenesis, looks at *in vivo* imaging of tumour angiogenesis and identifying biomarkers to establish drug efficacy. Chapter 13: *In vivo* imaging looks at imaging techniques. This clinically relevant chapter, examines various imaging modalities and describes how developments have shifted from the anatomic method to functional and molecular techniques. Chapter14: Identifying biomarkers to establish drug efficacy. Biomarkers, any test that will help to identify a population of patients is the subject of this chapter.

In summary, this text is well written, in a clear style, though obviously assumes prior knowledge of the subject. There are numerous clear black and white as well as colour plates, and there is a comprehensive list of references at the end of each chapter. ■

Reviewed by Dr Karin Baria,
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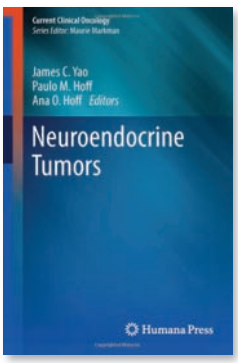
Neuroendocrine Tumours by Yao, Hoff and Hoff

By: JC Yao, PM Hoff and AO Hoff. Published by: Humana Press; 1st Edition. ISBN: 978-1-60327-996-3. Price: £144.00.



This text is a welcome addition to the *Current Clinical Oncology* series from Humana Press. Neuroendocrine tumours (NETs) are a very broad group of tumours, united by their origin from the diffuse neuroepithelial tissues. This can account for lesions that arise in many parts of the body including thyroid, adrenal, lung and gastro-intestinal tract.

One of the challenges in writing a book like this is to try and appeal to as many groups as possible as these tumours are managed by endocrinologists, gastroenterologists, surgical oncologists, clinical and medical oncologists and nuclear medicine physicians and, as such, require a true multidisciplinary approach. In the UK the United Kingdom and Ireland Neuroendocrine Tumour Society (UKINETS) has led the way in developing a multidisciplinary society, which has contributed to improvements in the standard of care for these tumours.

The book is extremely broad in its coverage and does include just about all of the neuroendocrine tumours, with the exception of pituitary and primary CNS lesions. In trying to be all things to all men it has to strike a balance between being sufficiently broad and comprehensive for the general reader, but at the same time providing sufficient depth for the specialist. To some extent it probably does slightly miss the mark. Nevertheless, as a handy lightweight reference it is an extremely useful addition both to the hospital library and the personal library of clinicians who manage these tumours.

It is often felt that Europe has led the way in the management of NETs, and this does seem to be reflected in the chapters within the book. Examples that highlight the trans-Atlantic difference include the chapter on imaging, where about eight lines are dedicated to the use of PET-CT imaging. The use of the 68Gallium-dotatate has made a huge impact in the management of NETs and, although still not widely available, it is expected to replace somatostatin receptor scintigraphy (Octreoscan) in the near future. Another area of difference is in the use of radiopeptide receptor therapy. Some reference is made to the use of meta-iodobenzylguanidine (MIBG) for the treatment of paragangliomas, phaeochromocytomas and carcinoids, but the half page devoted to the use of peptide receptor radiotherapy really does not do justice to what is now becoming a standard treatment in the management of these tumours. This probably reflects the limited availability of these compounds in North America and hence their relative lack of experience and usage.

For the medical management of many of NETs in their advanced state there are huge steps being made with the use of targeted anticancer agents, and the book has probably suffered from being written at a time when there had been significant leaps forward in the management of NETs, with constant reference made to the potential benefit of these agents. Good examples include vandetinib and cabozantinib (XL184) in medullary thyroid cancer, especially in some of the subtypes such as codon 918. It is most unfortunate that the timing has been disadvantageous.

Having said all that, there is much to commend in this book, and for an overview of these tumours it is a very readable reference book and a great asset to the library, which this reviewer anticipates he will dip in and out of regularly as a source of reference. ■

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Evolution of First-Line Therapy for Symptomatic Advanced-Stage Follicular Lymphoma

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Follicular Lymphoma (FL) is the most common of the low-grade lymphomas in the UK, affecting 2 per 100,000 population. Its incidence increases with age, with a median age of onset of 60-65 years [1]. The course of the disease is highly heterogeneous; the minority of patients have indolent disease with little or no progression over several years, and are monitored without treatment according to a 'watch and wait' policy. Others present with symptomatic disease requiring therapy and up to 25% of patients die following transformation of their disease to a more aggressive high-grade lymphoma [2].

The overall survival (OS) of FL patients has improved in recent decades. A North American registry study of >14,000 patients treated between 1978 and 1999 showed an increase in median survival of ~10% for patients treated in the later decade [3]. Although advances in supportive care may have contributed to better outcomes, recently published meta-analyses indicate an improved overall survival for newer approaches to therapy in this patient group. This article summarises the evolving treatment algorithm for patients with advanced stage FL and incorporate recent data on the application of new strategies for previously untreated patients.

Approach to first-line treatment

For >30 years active therapies have been available for the management of advanced stage FL. These include single agent cytotoxic agents (e.g. chlorambucil), combination cytotoxics (e.g. CHOP – cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone) and high-dose therapy with autologous stem cell transplantation (ASCT). More recently immunotherapy with monoclonal antibodies directed against the B-cell antigen, CD20 (rituximab) and radioimmunotherapy (e.g. 90Y-labeled ibritumomab tiuxetan) have been available. Well-designed clinical trials are available to inform the approach to treatment for the newly diagnosed patient. With a demonstrable improvement of all objective measures using these new approaches, including OS, the aim for almost all patients with FL is to optimise survival, with an important focus on quality of life and reduction of therapy-related toxicity. Simply abrogating symptoms is an inappropriate aim of treatment.

It is important to consider the biology of FL when deciding treatment. Patients with advanced stage disease are incurable, but may have a long period of asymptomatic disease before developing symptoms. There is no evidence that delaying therapy in asymptomatic patients is harmful. Comparing chemotherapy-based strategies with no treatment in this group, no improvement in overall survival was seen in the former. Using the latter approach, a significant number of patients can be spared the toxic effects of chemotherapy for prolonged periods. In the BNLI study, for example, comparing chlorambucil monotherapy or observation in asymptomatic patients, 40% over the age of 70 randomised to 'watch and wait' status either died from another disease without ever receiving therapy or had not received therapy at 10 years [4].

Patients with symptomatic disease or vital organ dysfunction require therapy (Table 1). They are treated with the expectation that the disease will follow a relapsing and remitting course, and may require several lines of therapy during the course of the disease over many years. Detailed discussion with the patient of this clinical approach is critical.

Several randomised control trials have demonstrated that the addition of rituximab to chemotherapy improves response rate and survival in this setting. A meta-analysis that included almost 1000 patients with previously untreated disease indicated a significant improvement in OS when rituximab was added to chemotherapy [5]. The estimated number needing to be treated with the combination to offset one death was 17 patients (95%, CI 13-33). The benefit to OS is independent of the chemotherapy used along with rituximab, although the selection remains controversial in some centres.

Improving outcomes for patients who respond to first-line treatment

Rituximab has been extensively investigated as an agent given repeatedly after induction therapy to delay the recurrence of symptomatic disease. There is a clear benefit of this pattern (i.e. rituximab maintenance) for those patients with relapsed FL treated with chemotherapy, with or without rituximab [6]. There is also evidence of the benefit of rituximab maintenance in previously untreated patients responding to chemotherapy alone. The Eastern Cooperative Oncology Group (ECOG)/Cancer and Leukemia Group B (CALGB) E1496 phase-III trial examined the effect of maintenance rituximab therapy given to patients with advanced-stage disease after first-line CVP without concomitant rituximab therapy [7]. A total of 237 patients were randomised to receive either rituximab subsequently every six months for four courses or simply observed. The four-year PFS of

Table 1: Standard indications for therapy in advanced stage FL patients.
Adapted from Ardeshna et al. (2003) [4]

Characteristic
Presence of B symptoms – fever, drenching night sweats, or unintentional weight loss of >10% of normal body weight over a period of six months or less
Local symptoms or compromise of normal organ function due to progressive nodal disease or extra-nodal tumour mass
Presence of symptomatic extra-nodal disease (e.g., pleural effusions, peritoneal ascites etc)
Peripheral blood cytopenias due to underlying lymphoma (i.e., absolute neutrophil count <1.0 x 109/L, hemoglobin ≤10 g/dL, and/or platelet count ≤100 x109/L)
Symptomatic splenic enlargement
Bulky disease, defined as a nodal or extra-nodal (except spleen) mass >7 cm in the greatest diameter

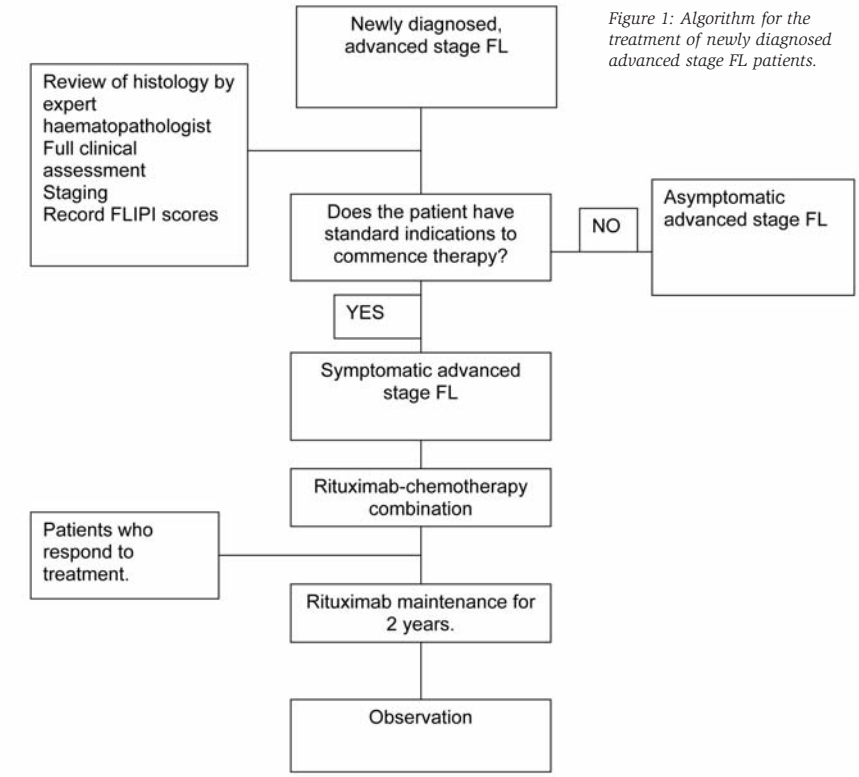

Figure 1: Algorithm for the treatment of newly diagnosed advanced stage FL patients.

56% and 33%, respectively, and four-year OS rates of 88% and 72%, respectively, favoured the rituximab maintenance arm since it provided some survival benefit.

The applicability of this information has been limited because chemotherapy alone is not the standard of care for newly diagnosed patients. Recently, however, the PRIMA (primary rituximab maintenance) trial reported on the benefit of two years of maintenance rituximab given to treatment-naive patients who had initially received a combination of rituximab and chemotherapy [8]. A single infusion of rituximab administered every 8 weeks after completion of induction treatment to responding patients prolongs predicted PFS, 74.9% (CI 71–79) in the rituximab maintenance group and 57.6% (CI 53–62) in the observation group after a median follow-up of 36 months. The time that the next lymphoma treatment had to be given was delayed and the quality of response achieved was also improved by maintenance rituximab; 71.5% (CI 67–75) in the rituximab maintenance group were in complete remission compared with 52.2% (CI 48–57) in the observation group. More patients in partial response at the time of randomisation became complete responders after two years in the rituximab maintenance group (72/139 [52%]) than those in the observation group (45/152 [30%]). The benefit of maintenance was seen across all age groups and FLIPI risk scores. This strategy was associated with a relative increase in the risk of infections (risk ratio 1.62; CI 1.35-1.96).

In any disease with a long natural history, it is essential to consider long-term safety issues with new strategies. Martinelli et al. [9] reported on long-term toxicity in an unplanned analysis of >200 patients who had received maintenance rituximab in earlier studies. After a median follow-up of almost 10 years, there were no unexpected cases of toxicity in those receiving two years of maintenance treatment with rituximab.

Other strategies have been applied to patients responding to first-line therapy. Radioimmunotherapy (RIT) consists of monoclonal antibodies loaded with radio-isotopes for the purpose of applying radiation therapy to tumours in targeted fashion. Ibritumomab tiuxetan has been studied in patients responding to first-line chemotherapy or rituximab chemotherapy combinations. In the FIT (first-line, indolent) trial, >400 patients responding to therapy were randomised to receive no further treatment or RIT as a single dose of 14.8 MBq/m^2 of ibritumomab tiuxetan [10]. After a median follow-up of 2.9 years, PFS increased from 13.5 months to 37 months in the RIT arm. In addition, 77% of those patients achieving PR after initial therapy converted to CR after RIT, which translates into an overall 87% CR rate for the RIT group. The toxicity of RIT was acceptable in this study, with a grade 3-4 infection rate of 8% after RIT compared to 2% in the controls. Concern about translating the results into clinical practice relates to the fact that the treatment offered to the majority of patients at induction is sub-standard. Only a small sub-group of patients in the FIT study received R-chemotherapy, so whether the benefit described above will apply to patients who receive standard of care remains unclear.

Interferon is an agent with immuno-modulatory effects that has been studied in treatment-naive FL patients responding to therapy. Although a survival benefit was reported in a meta-analysis for high dose therapy when combined with chemotherapy [11], no benefit was seen when given to patients as maintenance therapy following anthracycline-containing chemotherapy.

Conclusion

The outcome for patients with FL has improved in recent decades as a consequence of new therapies and advances in supportive care. Patients without well-defined indications for therapy should be monitored regularly, due to a lack of an overall survival benefit with studied interventions and the acceptability of observation to most patients (Figure 1). Those with symptomatic disease should receive rituximab in combination with chemotherapy. To prolong PFS, responding patients should be offered rituximab maintenance over two years. The goal of therapy for most patients will be to optimise quantity of life whilst maintaining quality of life, both of which are readily achievable in patients with newly diagnosed FL. ■

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Febrile neutropenia, severe neutropenia or thrombocytopenia requires dose delay or reduction. Patients with ALT or AST >3 x ULN or bilirubin >1.5 x ULN have a higher incidence of Grade 4 neutropenia and febrile neutropenia. Severe neutropenia may be managed with G-CSF or equivalent at the physician's discretion in accordance with relevant guidelines. Monitor closely for signs of peripheral motor and sensory neuropathy. Severe peripheral neurotoxicity requires dose delay or reduction. QT prolongation on Day 8 has been observed. ECG monitoring recommended in patients with congestive heart failure, bradyarrhythmias, if also receiving medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating eribulin and monitor during therapy. Eribulin should be avoided in patients with congenital long QT syndrome. No experience of using eribulin in combination with anti-HER2 therapy in clinical trials. Medicinal product contains small amounts of ethanol (<100 mg per dose). ***Drug Interactions:*** Concomitant use with substances which are inhibitors of hepatic transport proteins or with enzyme inducing substances not recommended. Exercise caution with concomitant use with substances metabolised by CYP3A4; avoid concomitant use if substance has a narrow therapeutic window. ***Pregnancy and lactation:*** Do not use during pregnancy unless clearly necessary. Contraception advised. Do not use during breast feeding. ***Effects on ability to drive and use machines:*** Do not drive or use machines if experiencing tiredness or dizziness. ***Undesirable effects:*** Adverse reactions reported with eribulin in breast cancer clinical trials: *Very common (≥1/10):* Neutropenia, leukopenia, anaemia; Decreased appetite; Peripheral neuropathy, headache; Nausea, constipation, diarrhoea, vomiting; Alopecia; Arthralgia and myalgia; Fatigue/asthenia, pyrexia. *Common (≥1/100 to <1/10):* Urinary tract infection, oral candidiasis, upper respiratory tract infection, nasopharyngitis, rhinitis; Febrile neutropenia, thrombocytopenia, lymphopenia; Hypokalaemia, hypomagnesaemia, dehydration, hyperglycaemia, hypophosphatemia; Insomnia, depression; Dysgeusia, dizziness, hypoaesthesia, lethargy, neurotoxicity; Lacrimation increased, conjunctivitis; Vertigo; Tachycardia; Hot flush; Dyspnoea, cough, oropharyngeal pain, epistaxis, rhinorrhoea; Abdominal pain, stomatitis, dry mouth, dyspepsia, gastrooesophageal reflux disease, mouth ulceration, abdominal distention; Alanine aminotransferase increased, aspartate aminotransferase increased; Rash, pruritus, nail disorder, night sweats, palmar plantar erythrodysaesthesia, dry skin, erythema, hyperhidrosis; Pain in extremity, muscle spasms musculoskeletal pain and musculoskeletal chest pain, muscular weakness, bone pain, back pain; Mucosal Inflammation, peripheral oedema, pain, chills, influenza like illness, chest pain; Weight decreased. *Medically significant but uncommon (≥1/1,000 to <1/100):* Pneumonia, neutropenic sepsis, oral herpes, Herpes zoster; Tinnitus; Deep vein thrombosis, pulmonary embolism; Interstitial lung disease; Hyperbilirubinaemia; Angioedema; Dysuria, haematuria, proteinuria, renal failure. ***Overdose:*** No known antidote. Closely monitor and manage with supportive medical interventions. ***Shelf-life:*** 4 years. Special precautions for storage: None. For storage conditions of the opened and diluted medicinal product, see SPC. ***Legal Category:*** POM ***Cost:*** Eribulin 0.44mg/ml 2ml vial: £313 per vial ***Marketing authorisation (MA) number:*** Eribulin 0.44mg/ml 2ml vial x 1: EU/1/11/678/001, Eribulin 0.44mg/ml 2ml vial x 6: EU/1/11/678/002 ***MA holder:*** Eisai Europe Ltd. ***Further information from:*** Eisai Ltd., Mosquito Way, Hatfield, Hertfordshire, AL10 9SN, United Kingdom. ***Date of preparation:*** March 2011

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* Locally advanced or metastatic breast cancer that has progressed following use of at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments[1]

Reference **1.** Halaven Summary of Product Characteristics. 2011 **2.** Cortes J *et al. Lancet* 2011; 377: 914 -23.

Date of preparation: May 2011 Job code: Eribulin-UK2053

Breast Cancer Stem Cells

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Despite the progress made in the early diagnosis and treatment of breast cancer, around 30% of all patients will develop recurrence of the disease, mostly in the form of metastatic tumours [1]. If patients are diagnosed early, conventional chemotherapy can initially control metastatic disease, however most patients will relapse over time [2]. Determining which of the cells in the tumour mass are most likely to give rise to daughter cells of a metastatic phenotype is an area of considerable research interest. Recent progress in our understanding of cancer biology has led to the identification of a sub-population of cells within tumours which have stem cell like properties [3]. There is growing evidence these cancer stem cells (CSCs) contribute to treatment failure due to intrinsic resistance to conventional therapies [4]. Therefore, the development of treatments which specifically target breast CSC could provide a new therapeutic approach aimed at curing the disease [5].

The cancer stem cell hypothesis

Until recently tumours were generally accepted to propagate according to the stochastic, model whereby a transformed cell would acquire an increasingly tumourgenic phenotype by accumulation of genetic mutations [6]. In this theory all progeny derived from the transformed cell would retain the potential to form new tumours (Figure 1A), however this idea is currently being challenged as there is growing evidence to support an alternative hierarchical CSC model. This new theory suggests that cancer originates from a mutated stem or progenitor cell within a tissue that acquires tumourgenic properties and is responsible for the initiation and maintenance of the neoplastic lesion [3]. In this model only a sub-set of CSCs within the tumour have the capacity to initiate new tumour growth (Figure 1B).

Cancer stem cells are aptly named because of stem cell like properties include the capacity to divide producing either daughter CSCs or progeny which can divide and form mature tumour cell types. Stem cells are hypothesised to be the tumour initiating cells within tissues because of two unique properties. Firstly, they have longer lifespan within the body allowing them to accrue the multiple somatic mutations necessary for cell proliferation at the same time the mutations also alter/abrogate key enzyme activity in pathways important for programmed (apoptotic) cell death. A second key property of CSCs is their capacity to form the multiple different mature cell types that have often been observed within tumours [7]. Although there is growing evidence supporting the CSC hypothesis, a recent study of breast cancers suggests that CSCs can also arise from the de-differentiation of mature cancer cells [8]. This finding supports the stochastic breast cancer model; however, further research will be required to determine whether both models for cancer initiation exist for different types of cancer.

CSC identification

The first evidence supporting the CSC hypothesis came from work that had been carried out on leukaemia [9]. In this early work leukaemic cells were separated according to the expression of protein markers of normal healthy stem cells. Only the sub-fraction of cells that expressed stem markers were able to initiate cancer when the cells were engrafted into immunocompromised mice [9,10]. Leukaemic cells that did not express stem cell markers were unable to engraft in mice. The methodology adopted in this study is now regarded as the gold standard for identifying CSC and similar findings using different combinations

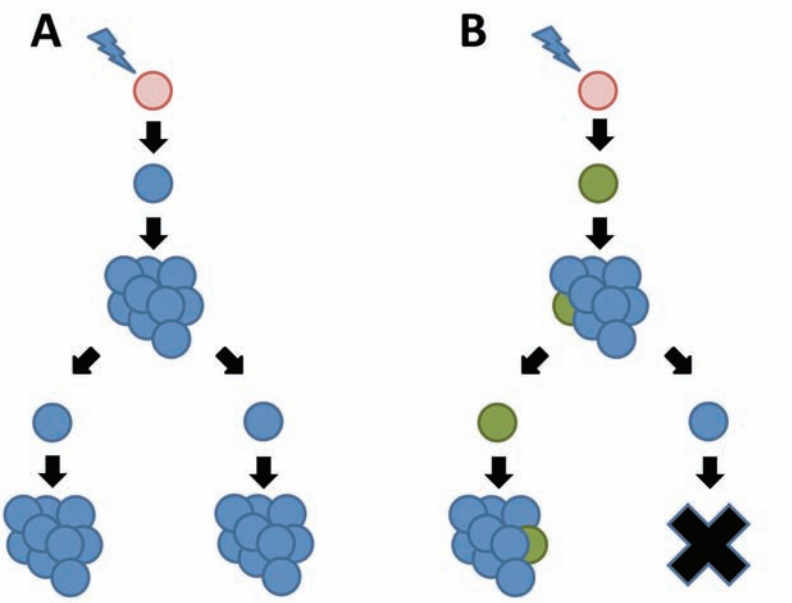

Figure 1: In the stochastic model of tumour initiation (A) all tumour cells have the same ability to initiate new tumours. In contrast the Cancer Stem Cell (CSC) model (B) proposes that a tissue stem cell becomes transformed into a CSC (green) which divides and differentiates to form a tumour mass (blue). Only the rare CSCs within the tumour mass are capable of initiating tumour growth at a new site.

of cell surface markers have been replicated in a wide range of solid cancers, including those from the brain [11], colon [12] and in osteosarcoma [13]. CSCs associated with breast cancer were first described in 2003 by Al-hajj, based on the surface markers $CD44^{+}CD24^{-/low}$ [14]. Since then other additional markers which can identify potential breast CSCs have been reported. These include the isolation of cells which exclude the Hoechest dye, the expression of the surface protein CD133 and the presence of the intracellular enzyme aldehyde dehydrogenase (ALDH) [15]. Additional research is, however, required to establish whether these markers identify the same sub population of CSCs within tumour specimens.

How CSC relate to breast cancer subtypes

Breast cancer is a heterogenous disease classified into a number of different subtypes, all with varying prognoses [16]. Breast cancer subtypes are often categorised on the basis of their expression of the oestrogen receptor (ER). ER positive tumours encompass the luminal subtypes with generally a more favourable prognosis, whereas the ER negative tumours include basal subtypes like HER2 and normal breast like tumours [16]. The clinical heterogeneity of breast cancer raises the question as to whether different subtypes contain distinct sub populations of CSCs responsible for the propagation and expansion of the tumour mass [17]. Studies with cancer cell lines indicate that this may be the case, as CSC expressing CD44 + CD24-/low are more closely related to basal like tumours [18]. In contrast, the intracellular enzyme ALDH was associated with CSCs from basal-like and HER2 positive tumours, whereas exclusion of Hoechest dye was associated with luminal type A CSCs [17].

CSC drug resistance

CSCs appear to have an intrinsic resistance to chemotherapy and radiotherapy. This is a property which has been implicated in treatment failure in a range of cancers [4,19]. In support of this theory is the enrichment of CSCs from tumour specimens resected after chemotherapy treatment of breast cancer patients [20]. The mechanisms enabling breast CSCs to resist the action of chemotherapy are only just starting to be understood. The expression of the membrane protein transporter ABCG2 in CSC is responsible for efflux of drugs from tumour cells, thus preventing the drugs from binding to their therapeutic targets [21]. In addition, the inhibition of the CSC marker ALDH sensitises breast cancer cells to chemotherapy and radiotherapy, suggesting that ALDH is also functionally important, allowing CSCs to become resistant to both of these treatments [22].

New therapeutic approaches which specifically target CSCs are beginning to show promising results. For example, a reduction in the CSCs of breast cancer was observed following neoadjuvant treatment with the tyrosine kinase inhibitor lapatinib [23]. Another drug showing promise as a treatment for CSC is salinomycin. This potassium ionophore resulted in a 100 fold greater cell death than paclitaxel [24], however further studies are required to assess whether salinomycin also targets the healthy stem cell population.

Metastasis

Metastasis is a complex process which we are only just starting to understand. Only a minority of the cells within a tumour have the capacity to migrate to distant organs and establish a new tumour [25]. Recent evidence suggests that CSCs possess the ability to form secondary tumours away from the breast cancer [26]. CSCs characterised as $CD44^{+}CD24^{-/low}$ cells in breast cancer have an invasive phenotype which is associated with an increased risk of metastasis formation [27]. An additional complexity of breast cancer metastasis is the organ-selectivity, for example, ER + tumours commonly migrate to the bone whilst ER- tumours have been observed to migrate and establish new tumours in visceral organs [17]. Although the reason for this preference is unknown it is thought that CSCs may play a role. This is an area which requires further research and is likely to be an active area in breast cancer research during the next decade.

Conclusion

The cancer stem cell theory is now widely accepted and there is growing evidence implicating CSCs as the driving force behind the growth and spread of breast cancer as well as playing a key role in treatment failure. CSCs can be identified by specific surface markers but additional markers are required to fully understand the role of CSC in different breast cancer subtypes. The resistance of breast CSCs to therapeutic regimens may be a reason for breast cancer relapse. As our understanding of the CSCs increases we will be able to design new treatments which selectively target the CSCs. Using drugs to target both the CSCs and mature tumour cells should lead to improved long term survival of patients suffering from this disease. ■

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Management of Brain Metastases: Patient Selection for Aggressive Local Management and the Role of Stereotactic Radiosurgery

The management of brain metastases remains challenging for oncologists. Brain metastases affect up to 40% of patients with cancer and, with improvements in systemic anti-cancer treatment and more sensitive imaging, this incidence appears to be rising [1]. Historically, the majority of patients with brain metastases were treated with whole brain radiotherapy (WBRT), but in recent years that conventional wisdom has been increasingly questioned. For many patients, prognosis is poor and there may be little or no benefit from subjecting them to the morbidity of WBRT if their symptoms can be controlled with corticosteroids alone. This is currently being investigated in lung cancer patients within the MRC QUARTZ trial, which is comparing WBRT with best supportive care [2]. Unfortunately, recruitment into this trial has been slow, suggesting that many oncologists may still have fixed ideas regarding the likely benefits, or otherwise, of WBRT. Interim results have been reported, with no apparent difference in overall survival.

On the other hand, there is a small group of patients with brain metastases in whom aggressive local management is very appropriate, either with neurosurgical resection or stereotactic radiosurgery (SRS), perhaps even a combination of both. Recognition of those patients who have a more favourable prognosis and are likely to benefit from a more aggressive approach is a regular challenge for neurosurgery and neuro-oncology teams.

Prognostic indices

In recent years, a number of prognostic scoring systems have been developed to facilitate management decisions in patients with brain metastases. The recursive partitioning analysis (RPA) score is determined by age, Karnofsky performance status (KPS) and status of systemic disease (Table 1) [3]. Based on these factors, patients are grouped into one of three prognostic groups, which were originally developed using retrospective data from the RTOG database, but have since been validated prospectively. The more recent Graded Prognostic Assessment (GPA) expands this to include the number of metastases as a fourth variable, and has four prognostic groups rather than three (Table 2) [4]. Other prognostic indices have been described, including the score index for radiosurgery (SIR) [5] and the basic score for brain metastases (BSBM) [6], but GPA was derived from the largest dataset (n = 1,960) and has been most widely used. Regardless of the index used, the proportion of patients in the most favourable prognostic groups, unfortunately, is small. Since the GPA index was first described, there have been a number of tumour-specific modifications to the system, most notably in breast cancer [7]. An eloquent comparison of the different prognostic indices noted that some tumour types are not well represented and gave ideas for future refinements [8].

Aggressive local management

With appropriate patient selection, there does appear to be a significant advantage in those managed with surgery or SRS. The benefits of neurosurgical resection have been demonstrated in a number of randomised trials, showing improved local control and overall survival [9,10,11]. More recent trials have

Table 1: RPA classification and prognosis

RPA Class	Description	Median OS
1	KPS >70, age <65, controlled primary disease	7.1 months
2	KPS >70, age >65 or uncontrolled primary disease	4.2 months
3	KPS <70	2.3 months

Table 2: GPA classification

GPA Score	0	0.5	1
Age	>60	50-59	<50
KPS	<70	70-80	90-100
Number of brain metastases	>3	2-3	1
Extracranial metastases	Present	-	None

Table 3: Prognosis according to GPA score

GPA Score	Median OS
0-1	2.6 months
1.5 – 2.5	3.8 months
3	6.9 months
3.5 – 4.0	11.0 months

Appropriate management of brain metastases remains a significant and regular challenge for neurosurgeons, neuro-oncologists and general oncologists

shown similar benefits with SRS. The RTOG 95-08 randomised trial, comparing SRS and WBRT with WBRT alone, for patients with 1 to 3 brain metastases and KPS greater than 70, demonstrated an overall survival benefit with SRS in patients with a single metastasis (6.5 v 4.9 months, $p = 0.0393$), regardless of other factors [12]. Those in the SRS arm were also more likely to have a stable or improved KPS at six months. In those with multiple metastases, only patients of RPA class 1 appeared to benefit. An earlier trial comparing SRS and WBRT to WBRT alone for 2-4 metastases used local control as the primary endpoint and was stopped early as a significant difference emerged. The local control rate was 92% with SRS with WBRT, but 0% for WBRT alone. Median time to local failure was 36 months in the SRS with WBRT group, compared with only six months with WBRT alone [13].

Those patients deemed suitable for aggressive local management of brain metastases are ideally younger patients with good performance status, 1 to 3 metastases and controlled systemic disease. A further group includes those with synchronous presentation with the primary or other metastatic disease, in whom there is a radical treatment option for the primary lesion, or treatment with a reasonable expectation of longer-term survival for metastatic disease. A good example of the latter is hormone-sensitive breast cancer, with which many patients can expect to survive for several years with appropriate systemic treatment.

The choice of neurosurgery versus SRS should be considered in the multi-disciplinary setting, with appropriate information sought regarding likely prognosis from extra-cranial disease. Neurosurgery and SRS have distinct advantages and disadvantages, with no evidence of superiority with either modality, as concluded by a Cochrane review in 2010 which found no suitable randomised trial comparing the two modalities in the context of metastatic non-small cell lung cancer [14]. For larger lesions, particularly those greater than 3.0cm diameter, surgical resection is generally considered to be the preferred option. Similarly, when there is a need for histological confirmation then resection should be favoured. On the other hand, for smaller or deep-seated lesions, or those in or near eloquent areas of the brain, the risks of surgical resection may be such that the non-invasive option of SRS is recommended. In some patients who undergo surgical resection, there may be an advantage in offering post-operative radiosurgery to the surgical bed, as discussed below. Neurosurgical resection is not discussed in any further detail here.

Stereotactic radiosurgery

Stereotactic radiosurgery (SRS) was developed, in 1951, by Swedish neurosurgeon Lars Leksell [15]. It utilises external three-dimensional reference points to locate small targets within the brain, allowing precise delivery of a single large fraction of radiation, or in some cases several smaller fractions. Leksell described radiosurgery initially using a 200kV x-ray machine, but in 1968 developed a Cobalt-60 gamma source unit, the Leksell gamma knife. Modern gamma knife units employ the same basic principles. Radiosurgery can also be delivered using a linear accelerator (LINAC), retro-fitted with micoMLC (multi-leaf collimator), or modern purpose-built radiosurgery equipment. LINAC-based SRS can be delivered using fixed beams, intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT).

Traditionally radiosurgery has required fixation of the head using screws, thus requiring patients to be planned and treated in one visit. Newer technologies allow treatment to be delivered using a removable thermoplastic shell and even frameless SRS is now becoming widely available. Whatever technique is used, the aim of SRS is to deliver a necrotising dose of radiation to a small volume of tissue, containing the target lesion and a minimal volume of surrounding normal tissue.

Metastatic brain lesions, first treated using radiosurgery in the early 1980s, have a number of characteristics which make them particularly suitable for SRS. They are usually discrete, well-circumscribed, spherical lesions. In most cases, they enhance vividly with intravenous contrast, facilitating target definition during treatment planning. Furthermore, in potentially radioresistant tumours with a low α/β ratio, such as melanoma, the large fraction size can overcome much of this radioresistance. There is even some evidence that some traditionally radioresistant tumours may actually respond better to SRS than so-called radiosensitive tumours [16].

Smaller lesions can safely be given higher doses, but with increasing diameter of the target lesion, the target volume and penumbra region increase significantly, resulting in a higher dose to surrounding brain. In lesions greater than 3.0cm many of the advantages of SRS are lost, although fractionated stereotactic radiotherapy may still be considered. SRS doses vary between centres and according to local protocols, but doses of 15-24Gy are typical, depending on the size and number of lesions being treated. The RTOG 95-08 protocol stated a marginal dose (to the 50% isodose line) of 24Gy for lesions up to 2.0cm, 18Gy for 2.1-3.0cm and 15Gy for lesions greater than 3.0cm [10].

Although most commonly used to treat single or oligo-metastases, some centres are now treating larger numbers of lesions, using triple-dose gadolinium MRI to maximise detection of smaller lesions. Even when large numbers of lesions are treated simultaneously, usually using gamma knife, the dose to surrounding normal brain can be kept low, when compared with WBRT [17].

Acute toxicities of SRS are usually mild and may include hair loss, local skin reactions, headache and nausea. Late toxicity needs to be carefully discussed with patients in advance, particularly in asymptomatic patients in whom SRS can trigger seizures, or cause pressure symptoms due to persistent oedema or radionecrosis. Earlier papers reporting outcomes following SRS for metastases tended to focus on tumour control and survival, undoubtedly under-reporting complication rates. A prospective review of 316 cases conducted at the M.D. Anderson Cancer Center, specifically to address complications, demonstrated a complication rate of 40%, the most common being new-onset seizures which occurred in 13% of cases [18]. Other important complications included haemorrhage (3%), the vast majority of which had melanoma, and hydrocephalus (1%), usually following treatment of cerebellar lesions near the fourth ventricle. The majority of severe complications occurred more than 30 days after SRS treatment. This 40% complication rate is much greater than previously reported in smaller case series and trials. Predictably, those with lesions in functional regions of the brain were more likely to develop complications. Patients with uncontrolled primary disease seem to be at more risk of complications. The toxicity and morbidity of SRS also appears to be greater in those patients receiving adjuvant WBRT following SRS.

Adjuvant whole brain radiotherapy

The next question, therefore, is that of adjuvant WBRT after local management

with either resection or SRS. Based on the older trials mentioned above, conventional wisdom has been to offer all patients adjuvant WBRT. However, the EORTC 22952-26001 trial compared WBRT with surveillance imaging in 359 patients following resection or SRS for 1 to 3 metastases and found that, although WBRT reduced the frequency of intracranial relapse, it failed to improve overall survival or functional independence [19]. Since WBRT adds significant morbidity, it has been suggested that after complete resection or successful SRS ablation, particularly of a single metastasis, many patients can be followed-up with regular brain imaging rather than immediate WBRT. A number of centres have adopted this approach, which requires careful discussion with the patient and a programme of regular imaging. The optimal imaging regimen has not been established, but an MRI scan at six weeks then every three months seems reasonable, with WBRT offered at relapse. This surveillance approach may be less attractive in those with multiple treated metastases and the authors of the EORTC trial continue to recommend adjuvant WBRT after local treatment of oligo-metastases. They also suggest that the surveillance option would be inappropriate in those who have had incomplete resection, those with a high risk of further intracranial disease (such as small cell lung cancer) or those who are having potentially curative treatment for their primary disease.

Surgery followed by radiosurgery

Recently there has been interest in treating highly-selected patients in a very aggressive manner with surgical resection followed by post-operative SRS or fractionated stereotactic radiotherapy (SRT) to the resection cavity. A retrospective review of 30 patients who underwent resection of 1-4 cerebral metastases, followed by adjuvant SRS or SRT, found that only 13% developed recurrence in the resection cavity [20]. However, 63% recurred elsewhere in the brain, the majority of whom received salvage WBRT at relapse. The 1-year overall survival was 51%. This approach of local management appears feasible, but patient selection is clearly going to be critical. In view of the high rate of recurrence elsewhere in the brain, perhaps there may even be a select group of patients who benefit from a triple modality approach of resection, followed by SRS to the resection cavity and adjuvant WBRT.

Summary

Appropriate management of brain metastases remains a significant and regular challenge for neurosurgeons, neuro-oncologists and general oncologists. While many patients are unlikely to benefit from any active intervention, and may be best managed conservatively with corticosteroids alone, there remains a role for WBRT in younger, fitter patients, particularly those for whom effective systemic treatment options remain. Furthermore, there is clearly a smaller, select group who benefit from aggressive local management with surgical resection or SRS and all potential cases should be discussed at a neuro-oncology multi-disciplinary meeting.

The choice of treatment will depend on the age and fitness of the patient, co-morbidities, the presence or absence of other sites of disease, the number and location of brain metastases and the nature of the underlying tumour. Patients deemed suitable for aggressive local management, i.e. those who have lesions less than 3.0cm, multiple lesions, surgical contra-indications, or with lesions in deep or eloquent parts of the brain, are likely to be offered SRS. Patients with single lesions greater than 3.0cm, in non-eloquent brain, or posterior fossa lesions, are more likely to be offered resection. Resection may also be preferred where there is a need to confirm the histological diagnosis. Even in less fit or older patients, SRS may be worthwhile for a single brain metastasis, although it is probably inappropriate for multiple metastases in such patients.

The role of adjuvant WBRT remains contentious and needs careful discussion with the patient – those who do not receive adjuvant WBRT will need an agreed surveillance imaging schedule, such as that described above. The utility of post-operative SRS to the resection cavity is also debatable, but may be considered on an individual patient basis.

SRS is, therefore, an important part of the armoury in the battle to effectively treat brain metastases, and all oncology units should have access to this treatment option for appropriate patients. ■

...there is a small group of patients with brain metastases in whom aggressive local management is very appropriate

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Smart Money's on Evidence-Based Medicine:

A Consumer's View on Incidental Bilateral Oophorectomy at the Time of Hysterectomy for Benign Conditions

Christine A Larson, Ph.D.
University of Kentucky, Lexington, Kentucky.

The author has twelve years of business development experience for Fortune 500 firms in the pharmaceutical and financial services industries and recently completed doctoral work in evidence-based medicine at the University of Kentucky.

Patents are pending on the health solutions developed and will be commercially available to assist other consumers who experience similar health outcomes after undergoing this surgical procedure.

The dissertation upon which this article is based: "Evidence-Based Medicine: An Analysis of Incidental Bilateral Oophorectomy at Time of Hysterectomy for Benign Conditions," is considered to be the first scientific analysis of this surgical procedure conducted by a former patient.

"Alternative Medicine," (2007), the author's first publication, introduced the concept of evidence-based medicine to the US consumer by exploring the science underlying both alternative and conventional medicine, with issues to consider in its absence. Medical reviews and endorsements on preliminary research in evidence-based medicine can be accessed at the company website: www.savvyconsumerguidetohealthcare.com

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The Chinese translation for the word crisis is 'opportunity riding on dangerous winds.' The dangerous economic winds we find ourselves in provide an opportunity to shed light on issues involving healthcare, using the sub-prime debacle as an illustration. The sub-prime debacle largely occurred because fundamentals of responsible mortgage-lending practices were ignored:

- First, do not lend money to those who cannot repay.
- Second, do not purchase homes you cannot afford.

Sub-prime mortgages were loans based on false fundamentals, making them a type of 'bogus stock'. Financial institutions and investment banks across the country proceeded to 'make a market' in this 'bogus stock', with remarkable success. When the real estate market declined, mortgage payments mushroomed, customers could not afford monthly payments, foreclosures escalated, banks became saddled with bad debt that could not be absorbed and financial institutions were threatened, some folded, putting the economy itself at risk.

When fundamentals of responsible practices in any industry are ignored, the outcome is not favourable, as the sub-prime debacle illustrates. But this phenomenon is not isolated to financial institutions and banking, however. Fundamentals exist in every industry that provide a basis for responsible practices, be it finance and mortgage lending, clinical trials and pharmaceuticals, or therapies used in healthcare. In the pharmaceutical industry, when science is ignored or minimised, as it was in the case of Vioxx, outcomes will not be favourable for the manufacturers or the end-users, the patients.

Cardiovascular effects were evidenced in early clinical trials of Vioxx, but the senior scientist was prohibited from releasing the evidence due to its proprietary nature. The drug was later approved by the FDA and released onto the market, resulting in a 'sudden spike in cardiac deaths' among members in a managed-care company's database. The common denominator was Vioxx. The drug was later recalled at the request of the FDA.

Pharmaceutical products or treatments used in healthcare are only as good as the fundamental science that supports them. Evidence-based medicine is the foundation of responsible medical practice.

Sackett (1996) defines evidence-based medicine, as: "...the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients." Science is limited, however, and decisions are required, often in the absence of proper scientific guidance. What are the implications of this absence of science? Samuel Nussbaum (2003), chief medical officer of Anthem, Inc, at the Disease Management Congress stated that: '... < 50% of medicine is science-based,' i.e. half of medical practice has no proof of efficacy through randomised clinical trials. David Eddy (2006), a former Stanford heart surgeon, now health economist, noted that 20-50% of medicine is evidence-based, which means that 50-80% of medical practice lacks scientific proof of efficacy through randomised clinical trials. The implications are that decisions are required in the absence of scientific support and assumptions are made. Assumptions, however, are not a substitute for scientific proof of efficacy.

In a 'BusinessWeek' (2006) feature story, 'Medical Guesswork', a US corporate executive noted that: "There is a massive amount of spending on things that really don't help patients and even put them at greater risk. Everyone that's informed on the topic knows it, but it is such a scary thing to discuss that people are not willing to talk about it openly" – the proverbial elephant in the room. This lack of evidence-based medicine often creates a high-stakes, high-cost 'trial and error' scenario that results in unresolved health problems, perhaps compounded by a decline in health status. With reference to protocols used in clinical medicine, the 50-80% that lack scientific support encompass all clinical specialties, with obstetrics and gynaecology being no exception.

Post-operative health outcomes following a hysterectomy with an incidental bilateral oophorectomy for treatment of non-cancerous uterine fibroids was the impetus for this research. Of particular interest was the scientific support for this surgical procedure in women without risk factors. A literature review indicated significant scientific gaps that existed with both procedures and scant long-term data on outcomes, particularly troublesome from the patient's perspective. AHRQ (2001) concludes: '...a broad range of patient outcomes need assessment...it is critical to understand the effects of treatment (or time) on the presenting symptoms and to measure the value of particular outcomes in individual women.' AHRQ's (2001) summary statement of particular relevance: '...very few studies provide information...on the symptoms that led women to seek treatment in the first place or in the long-term outcomes that effect the patient's quality of life.'

Culiner (1958) first raised questions on the use of incidental bilateral oophrectomy at the time of hysterectomy for benign conditions. Gibbs (1971) popularised the procedure, claiming 'prophylaxis is the cure' in preventing deaths from ovarian carcinoma, which is difficult to detect and, when found at late stages, has an 80% mortality rate. Clinical decision-making incorporates a risk-benefit ratio in determining the usefulness of a treatment in a particular case. The risk profile of this prophylactic surgical procedure includes Culiner's (1958) reference to: '...an endocrine imbalance that cannot be corrected artificially,

cardiovascular effects and osteoporosis.' Epidemiologists, public health experts and gynecologists over the last 55 years have added adverse health outcomes of an increasingly severe and debilitating nature to this risk profile.

Colditz (1987) reports a higher incidence of coronary vascular disease. Shoupe (1999) reports a higher incidence of dementia, depressive and mood disorders, increased incidence of coronary vascular disease and sexual dysfunction. Parker et al. (2005, 2009) reports a higher incidence of heart disease, cancer and stroke, all-cause mortality and premature death, as did Schuster et al. (2008). Rocca et al. (2006, 2007, 2008) reports a higher incidence of cognitive decline, dementia and neurological disorders.

This researcher's initial post-operative health outcomes included high blood pressure and cholesterol, pre-diabetes, and weight gain and may in fact serve as a prototype for many women post-operatively who undergo this surgical procedure. That downward health trajectory was reversed through proprietary medical research, with my health fully restored in 2005. However, as Parker et al. (2005, 2009), Rocca et al. (2006, 2007, 2008) and Schuster et al. (2008) point out, that initial health trajectory, for many, will continue its downward spiral, with end-points of chronic disease, disability, and premature death.

Culiner (1958) said it best, a half-century ago: "If the ovaries appear normal, of there is no history of carcinoma, if the patient understands and accepts the risks, the ovaries usually can be conserved at hysterectomy for benign conditions." ■

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Journal Reviews

Head & Neck

Minimally invasive video-assisted thyroidectomy 2.0: Expanded indications in a tertiary care cancer center

Background: Minimally invasive video-assisted thyroidectomy (MIVAT) advantages include a smaller incision, less extensive surgical dissection, improved visualisation secondary to rigid fiberoptics, and decreased postoperative pain. The aims of our study were to report our experience using expanded indications of MIVAT.
Methods: A retrospective chart review of a single surgeon's initial experience was carried out at a tertiary academic cancer center.
Results: In all, 53 patients were identified, of whom 40 underwent total thyroidectomy and 13 underwent hemithyroidectomy. Thyroid volume, nodule size, incision length, and surgical time were all examined. Most common pathology was well-differentiated papillary thyroid cancer (69.8%): 42% of patients had evidence of thyroiditis found on pathology; 17% of patients had temporary vocal cord paralysis, with only 1 case of vocal cord paralysis persisting >6 months (1.9%). Six patients (11%) experienced temporary hypocalcemia, requiring postoperative calcium supplementation; no patients experienced permanent hypocalcemia.
Conclusions: The use of MIVAT with expanded indications shows complication rates comparable to those of traditional open thyroidectomy.
Reviewer's opinion: An interesting paper from Memorial-Sloan Kettering Cancer Center looking at MIVAT for thyroid cancer management. Paper shows safety of MIVAT technique in there hands in a small group of patients. It is popular in certain centers around the world. I feel one can still do thyroidectomy through a small incision without the need for using the MIVAT and producing similar cosmetic results.– MD
Head & Neck Minimally invasive video-assisted thyroidectomy 2.0: Expanded indications in a tertiary care cancer center.
Kim AJ, Liu JC, Ganly I, Kraus DH.
Head & Neck
2011;33(11):1557-61.

Transoral laser microsurgery as primary treatment for advanced-stage oropharyngeal cancer: A united states multicenter study

Background: Nonsurgical modalities are sometimes advocated as the standard of care for advanced oropharyngeal tumours. Oncologic and functional results have been modest. The aim of our study was to evaluate outcomes of a minimally invasive approach, using transoral laser microsurgery (TLM) as the primary treatment for advanced oropharyngeal carcinoma.
Methods: A prospectively assembled database of 204 patients with American Joint Committee on Cancer (AJCC) stages III and IV tonsil or tongue base cancer, treated primarily with TLM during 1996–2006 at 3 centers with minimum 2-year follow-up was analysed. Survival, locoregional control, and swallowing status were recorded.
Results: Mean follow-up was 49 months and 79.4% of patients were alive. Three-year overall survival, disease-specific survival, and disease-free survival were 86%, 88%, and 82%, respectively. Local control was 97%, and 87% of patients had normal swallowing or episodic dysphagia.
Conclusions: TLM as a primary treatment for advanced oropharyngeal malignancy confers excellent survival and swallowing proficiency.
Reviewer's opinion: The authors conclude that TLM is highly effective primary treatment option for management of advanced stage oropharyngeal cancer especially in the presence of HPV-positive biomarkers. The paper shows improved survival with adjuvant therapy. The addition of chemotherapy to radiotherapy was not associated with significant gain than radiotherapy alone. Therefore 83% was not exposed to risks of chemotoxicity. – MD
Haughey BH, Hinni ML et al.
Head & Neck
2011;33(12):1683-94.

Neuro-Oncology

SOX 2 dependent sub-population in Glioblastoma

Glioma stem-like cells, such as those identified in glioblastomas, have been shown to have the potential for self-renewal, cell division and multi lineage differentiation. However, the origin of these cells and their molecular phenotype are not yet fully characterised. Of particular importance may be tumour suppressor genes such as P53, PTEN and NF1. In this study the authors characterised 11 high grade glioma cultures in terms of their pattern of gene expression and response to two tyrosine kinase inhibitors targeting PDGFR and IGF-1R (Imatinib and NVP-AEW541). Two genetically distinct subgroups (Type A and Type B) were identified with differential expression of soluble proteins, extracellular matrix proteins (ECM) and transcription factors. Interestingly all of the type A cultures were GFAP positive whereas type B cultures showed high expression of ECM proteins. Furthermore, lineage specific markers such as GFAP, CXCR4 and EAAT1 were more highly expressed in Type A cultures than in Type B cultures which expressed CNP, PDGFRB and Laminin. There was no differential expression of the stem cell markers nestin and BMI1 between the two subsets however SOX2, another stem cell marker, was highly expressed in type A cultures. This was confirmed using immunofluorescence which showed exclusive expression of SOX2 in type A cells *in vitro*. Analysis of gene expression in two sets of clinical glioblastoma specimens (n=138) identified a similar pattern of gene expression in different tumour samples. Tissue from which the Type A cultures were derived formed *in vivo* tumours in SCID mice in all cases (8/8) whereas only 4/12 formed tumours in type B highlighting the increased tumourigenicity of the type A subgroup. Furthermore, type A cultures have an increased propensity to develop neurospheres which was inhibited by SiRNA mediated downregulation of SOX2. SOX 2 downregulation also resulted in increased sensitivity to treatment with TKIs with an additive effect when TKIs were given in combination.
Reviewer's opinions: This study identifies two genetically distinct subpopulations within a set of glioblastoma cultures, both displaying expression of stem cell markers. One subset appears to be enriched for SOX2 and is both neurosphere forming *in vitro* and tumourigenic *in vivo*. Furthermore, their subsets suggest some similarities between the recently described classical, proneural and mesechymal subsets of glioblastoma. The authors also highlight a novel way of overcoming resistance to TKIs highlighted in previous studies by combining both treatments. – SB
Identification of a SOX-2 dependent subset of tumour and sphere forming glioblastoma cells with a distinct tyrosine kinase inhibitor sensitivity profile.
Hagerstrand D, He X, Lindh MB, Hoefs S, Hesselager G, Ostman A, Nister M.
Neuro-Oncology
2011;13(11):1178-91.

Diary of Events

To have your event listed in the Oncology News diary E: Patricia@oncologynews.biz by February 5th 2012.

2012

February

NEW
Walk Around the World for Brain Tumours
1 January-31 December 2012
E: kathy@theibta.org
W: www.theibta.org

NEW
Communication in Cancer Care
10, 11, 24, 25 January & 8 February 2012; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

NEW
Lymphoedema: Diagnosis, Assessment & Risk Reduction
10-13 January 2012; Glasgow, UK
Mrs Margaret Sneddon, Programme Director,
Tel: 0141 330 2071/2072,
E: lymph@glasgow.ac.uk
W: http://www.gla.ac.uk/departments/nursing/

Communication in Cancer Care
10, 11, 24, 25 January & 8 February 2012; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

NEW
113th Meeting of the British Neuropathological Society (BNS) featuring a Symposium: "Recent Advances in Understanding Brain Tumours"
11-13 January 2012; London, UK
W: http://www.bns.org.uk

NEW
Chemotherapy in Cancer Care
11, 12, 13, 26 & 27 January 2012; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

Lymphoedema: Diagnosis, Assessment & Risk Reduction
17-20 January, 2012; Newcastle, UK
Mrs Margaret Sneddon, Programme Director,
T: +44 (0)141 330 2071/2072,
E: lymph@glasgow.ac.uk
W: http://www.gla.ac.uk/departments/nursing/

NEW
Manual Lymphatic Drainage: Leduc Method
18, 19, 20 January, 8, 9, 10 February & 1 March 2012; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

NEW
Masterclass - Breast cancer genetics
19 January 2012; London, UK
E: nursetraining@breastcancercare.org.uk

NEW
Cancer care; The GP, the patient and the oncologist
23 January 2012; London, UK
Ruth Threadgold,
T: +44 (0)20 7290 3942
F:+44 (0)20 7290 2989
E: oncology@rsm.ac.uk

Managing Complicated Lymphoedema Casley-Smith DLT (3 parts)
24-27January, 6-9 March, 6-8 June, 2012; Glasgow, UK
Mrs Margaret Sneddon, Programme Director,
T: +44 (0)141 330 2071/2072,
E: lymph@glasgow.ac.uk
W: http://www.gla.ac.uk/departments/nursing/

Radiation Protection Masterclass
25 January 2012; London, UK
E: conference@bir.org.uk

10th BTOG Conference 2012
25-27 January, 2012; Dublin, Ireland
E: dawn.mckinley@uhl-tr.nhs.uk
W: www.btog.org

Renal and Bladder Cancer 2012
26-27 January 2012; London, UK
Jackie Ogden
T: +44(0)20 7501 6762
W: www.mahealthcareevents.co.uk/renalbladder2012

NEW
IVth Symposium on Neuro-oncology in Practice - Brain Tumors: Now is the Future!
27 January 2012; The Hague, Netherlands
W: http://www.soc-neuro-onc.org

February

Controversies and Uncertainties in the Radiotherapy of Early Breast Cancer
2 February 2012; London, UK
E: conference@bir.org.uk

Magnetic Resonance Imaging in Clinical Obstetric Practice
3 February 2012; London, UK
E: conference@bir.org.uk

NEW
Mesothelioma Practice in Cancer Care
E-learning activities over 9 weeks commencing 6 February 2012; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

NEW
Teleconference - Older people with breast cancer
9 February 2012
E: nursetraining@breastcancercare.org.uk

NEW
15th Biennial Canadian Neuro-Oncology Meeting
9-11 February 2012;
Vancouver BC, Canada
W: http://www.soc-neuro-onc.org/en/cev/56

NEW
Rare Cancers Conference
10 February 2012; Brussels, Belgium
W: http://www.esmo.org/events/rare-cancers-conference-2012.html
E: longo.francesca@esmo.org
T: +41 (0)91 973 19 25

NEW
Foundations in Cancer Care
13, 14, 15, 16 & 17 February 2012; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

Lymphoedema: Specialist Service Development
14-17 February, 2012; Glasgow, UK
Mrs Margaret Sneddon, Programme Director,
T: +44 (0)141 330 2071/2072,
E: lymph@glasgow.ac.uk
W: http://www.gla.ac.uk/departments/nursing/

NEW
BUG: "What's New - What's Changing in Prostate Cancer?" One-day meeting
17 February 2012; London, UK
Janis Troup
T: +44 (0) 203 142 6491
E: janis.troup@rightangleuk.com

Breast Cancer Care
20, 21, 22, 23 & 24 February 2012; London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

Excellence in Oncology 2012
22-25 February, 2012;
Istanbul, Turkey
W: www.excellence-in-oncology.org

Connected – National Advanced Communication Skills Training
22, 23 & 24 February 2012;
London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

Rehabilitation in Cancer Care
23–24 February 2012;
Manchester, UK
W: www.christie.nhs.uk/pro/education/events
E: education.events@christie.nhs.uk

Gynaecological Cancer Care
27, 28, 29 February, 1 & 2 March 2012 ;London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

BSG Conference 2012
29 February – 2 March 2012;
Oxford, UK
W: www.bsgconference.org.uk

March

NEW
Late Effects in Cancer Survivors - 4th biennial Sheffield meeting
8-9 March 2012; Sheffield, UK
E: lateeffects@sheffield.ac.uk

NEW
International Congress on Targeted Anticancer Therapies (TAT 2012)
8-10 March 2012;
Amsterdam, The Netherlands
W: http://www.tatcongress.org

ESMO Conference on Sarcoma & GIST
9-10 March 2012; Milan, Italy
W: www.esmo.org/events/sarcoma-gist-2012-conference.html
E: conference@esmo.org
T: +41 (0)91 973 19 26

Palliative Care in Cancer
12, 13, 14, 15 & 16 March 2012;
London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

Stem Cell Transplantation in Cancer
12, 13, 14, 15 & 16 March 2012;
London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

Chemotherapy in Cancer Care
12, 13, 21, 22 & 23 March 2012;
London, UK
T: +44 (0) 20 7808 2900
E: school@rmh.nhs.uk
W. www.royalmarsden.nhs.uk/school

NEW
Sylvia Lawler prize meeting
14 March 2012; London, UK
Ruth Threadgold,
T: +44 (0)20 7290 3942
F:+44 (0)20 7290 2989
E: oncology@rsm.ac.uk

9th Palliative Care Congress
14-16 March 2012; Newcastle, UK
W: www.pccongress.org.uk
T: +44(0)1489 565475

BTOC 11 – Biological Therapy of Cancer
14-16 March, 2012; Munich, Germany
http://www.bdaoncology.org/pages/pv.asp?p=bda5

Spectroscopic Tools for Bladder Cancer Diagnostics and Research

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Diagnostic tests for bladder cancer rely on biochemistry (for haematuria, if not macroscopic), immunohistochemistry, direct visual inspection or imaging, histology of biopsy material and cytology of cells in urinary sediment [1]. The use of non-contact scanning to obtain surface spatial, deeper structural and biochemical information is particularly attractive *in vivo* and can also be applied to exfoliated cells in bulk or individually. There is a constant drive in medicine towards less invasive procedures that produce spatial as well as biochemical information. Spectroscopy offers the possibility of an 'optical' biopsy, using the word optical in its loosest sense, to mean 'wave mediated' where the waves in turn can be electromagnetic, particulate (due to the de Broglie wavelength of entities like electrons or neutrons) or mechanical (sound). In some parts of the electromagnetic spectrum we are comfortable with wave-particle duality, visible light waves and photons being the obvious example. In other areas one concept tends to dominate, somewhat to the confusion, or at least irritation, of those steeped in alternative nomenclature. The same applies to wavelengths, wavenumbers and energy levels.

Different systems reveal spatial information with a resolution inversely related to wavelength and biochemical information dependent on the nature of the interactions between the afferent radiation and molecular bonds in the target. Spectroscopy involves observing and making measurements of the interaction between matter and radiation where the efferent radiation differs from the incident radiation by virtue of absorption, scattering – either elastic (e.g. x-ray crystallography) or inelastic (Raman scatter), induced emissions (fluorescence), impedance or reflectance (acoustic spectroscopy or ultrasound) and resonance (MRI). All of these have existed in laboratory situations as non-imaging chemistry tools for decades before being directed to medical biochemistry and imaging.

It is advances in digital technology and computing power that have enabled the application of Fourier transform mathematics and sophisticated multivariate analyses such as principal component analysis, reviewed for near infra red, but generally applicable by Reich [1], to the study of biological material. The latter may range from cell cultures to *in vivo* clinical investigations and progressed from the chemistry of extracts to spatially defined chemistry, sometimes in real time, sometimes in three dimensions.

Most of these methods have been applied to bladder cancer problems [2], some have advanced to clinical acceptance as *in vivo* diagnostic aids. Others remain, for the time being, as procedures being applied to *ex-vivo* resection material or trialled in model living systems ranging from cultured cell lines to xenografts.

The basic product of spectroscopy is a plot of the selected measurement, be it transmittance, reflectance or absorbance, against wavelength or wavenumber. Biologists tend to be more comfortable with wavelength (in nm), professional spectroscopists with wavenumber (as cm-1). If collected in an array, these can be built into images, often derived from selected features of the plot, corresponding to specific molecular bonds or characteristics.

Bladder cancer has several characteristics that can be exploited for the application of emerging technologies. It is, at least in its early stages, superficial (non-muscle invasive) and on a surface which is easy to access endoscopically and from which cells as well as soluble molecules are shed into the urine and available in quantity for study.

We will summarise recent published advances in this area, eventually focussing on infra-red spectroscopy and imaging, which is currently one of the least developed technologies in the context of bladder cancer. This technology has the potentially advantageous feature that the fundamental vibrations and associated rotational-vibrational features of many metabolically important chemical bonds lie in the so-called "fingerprint region" (1450-600 cm-1, 6896-16666 nm) of the mid-range infra-red spectrum (usually set between 4000–400cm − 1, 2500-25000 nm). There are two aims discernible in the following investigations; firstly the differentiation of normal or benign from malignant cells or tissues, and secondly

Spectroscopic analysis and imaging utilising diverse wave forms can provide 'optical biopsy' information on bladder cancer in situ and insights into ongoing metabolism of cellular material *in vitro*

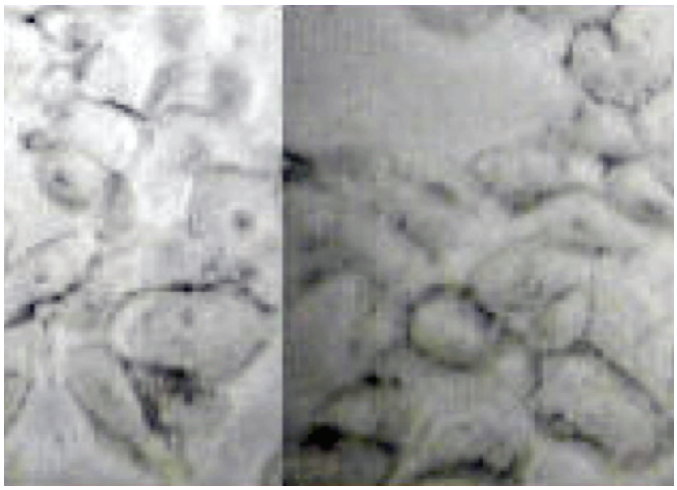
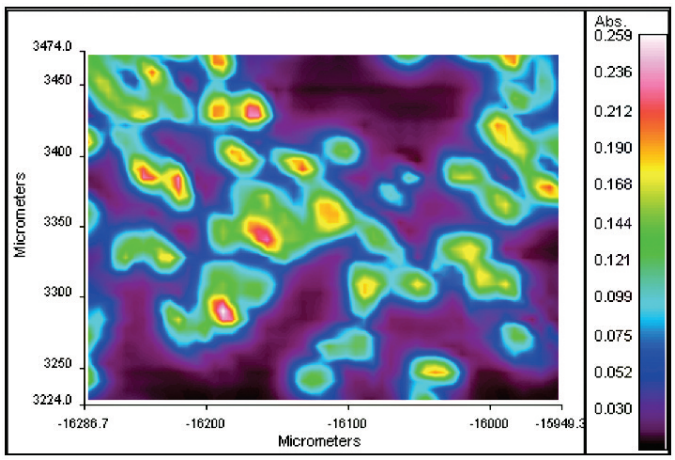


Figure 1a (above): Brightfield view of field for infrared imaging Figure 1b
Note the selection is from a tiled composite image. The picture quality is inferior to normal microscopy due to the arrangements for infrared analysis.
MGH-U1 urothelial cancer cells grown and fixed in situ on MirrIRTM reflective slide.

Figure 1b (below): FTIR image (mid range IR) of cells in Figure 1a.
Total absorbance is depicted according to the look-up colour scale shown.



more sophisticated biochemical distinctions to do with grading and/or prognostication.

Fluorescence from photosensitising drugs such as 5-aminolevulinic acid (ALA) for imaging superficial bladder cancer to improve resection [3] or for photodynamic therapy is well established. This is not spectroscopy per se, in that the excitation and emission wavelengths are known in advance and used in isolation, but they are grounded in spectroscopic theory. It may become true for some of the systems below that, once useful features are defined and their reproducibility accepted, they too may be so simplified for rapid clinical use, without the acquisition of complete spectra on each occasion.

Raman spectroscopy has been a popular field of research. An *in vivo* feasibility study was reported in 2010 [4], yielding data that, on multivariate analysis, could distinguish normal from cancerous tissue and showed some evidence of trends in amino acid composition and DNA quantitation with the stage of the disease. In response to concerns over the strength of Raman signals a further study [5], using *ex-vivo* bladder tissue, worked on combining fluorescence diagnostic procedures using ALA, which alone gives strong signals but modest sensitivity, with Raman spectroscopy, to achieve a better diagnostic result (despite ALA altering the Raman spectra expected from untreated tissue).

Another fluorophore being trialled for bladder cancer identification, currently using model systems such as xenografted cancer cells in immunosuppressed rodents or chick chorioallantoic membranes, is chlorin e6 [6], one of a group of large molecules derived from chlorophyll.

A twist on Raman spectroscopy, applied to live or fixed tumour cells in suspension, is the use of 'Raman Tweezers' [7]. The phrase is arguably a bit of a misnomer. Optical tweezers create a laser light gradient over a very small area into which microscopic dielectric particles (e.g. cells) may be trapped spatially in their suspending medium. These are then available for relatively time-consuming spectroscopy. The immobilisation and spectroscopy are achieved at different wavelengths. This has been trialled on cell lines, but has potential application in urine cytology.

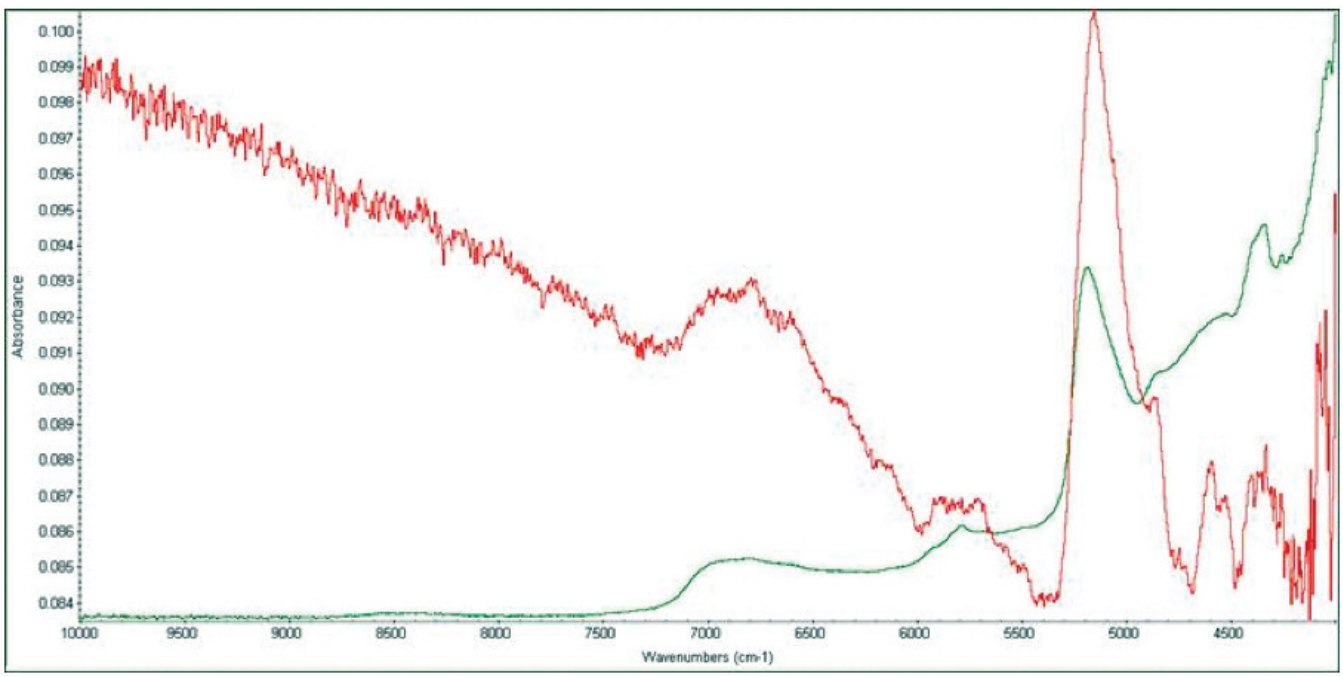


Figure 2: Near infrared spectra from cells and isolated nuclei
Two spectra, one from a dried unfixed cytospin of RT112 urothelial cancer cells (red) and a comparably thick cytospin preparation of isolated nuclei from the same passage. In this extreme example, the spectra are clearly different, without recourse to PCA analysis. Wavenumbers descending along x-axis from left: absorbance on y-axis.

Nuclear magnetic resonance (NMR) is familiar in its imaging form (MRI), but as a virtual biopsy method is still experimental or under development. This 'metabolic profiling' applied to urine is, along with mass spectrometry, reviewed by Van [8]. The application of two-dimensional variants on NMR techniques to live cancer cells *in vitro* has also been described [9]. As with Raman scatter, NMR has been combined with fluoresce in the form of (autofluorescent) quantum-dot capped magnetite (Fe2O4) nanorings, so far for *in vitro* intracellular imaging, but with a view to eventual clinical use, including potential as a therapeutic delivery system [10].

Optical spectroscopy encompasses a range of techniques – anything relying on the reflectance or scatter of light, usually at the more penetrating longer wavelengths. Diffuse reflectance optical spectroscopy, along with spontaneous or photosentitiser-related fluorescence, can be used to distinguish healthy from pathological tissue in model systems [11,12]. It can be developed further into optical coherence tomography, using time-of-flight information from light transmitted through or reflected from internal structures. The resulting images look not unlike the more familiar ultrasound scans, which after all work through similar principles though with a qualitatively different type of wave-form. There is also a publication, unfortunately in Chinese, the abstract of which suggests that diffuse reflectance spectra from this type of scan have been obtained *in vivo* from bladder cancer patients [13].

Infrared spectroscopy is of particular interest because of its ability to provide a molecular signature of the material being investigated, with the fingerprint region of the mid-range spectrum being where most biologically important molecules have characteristic absorption peaks. Near infrared radiation has the advantages of penetrating conventional substrates such as glass, allows direct estimation of the amount of material present and has greater resolution potential for imaging, due to its shorter wavelength. It is, however, not such a precise chemical tool as it excites only the harmonics or overtones of the vibrations captured by mid-range absorption.

Mid-range FT-IR has been applied to exfoliated cells recovered from the urine of bladder cancer patients. Multivariate analysis distinguished individual cell according to their spectra, correlating well with conventional cytology [14]. It has also been used in studies yet to be published to image cultured MGH-U1 bladder cancer cells (Figure 1).

Near infrared spectroscopy applied to cells is currently one of our areas of interest. It can be made to distinguish between cellular components as illustrated in Figure 2, where a spectrum from a dried but unfixed cytospin of whole RT112 cells is overlaid with a spectrum from a similar preparation of isolated nuclei from the same harvest of cells.

Reviews of the limitations of current cytologically based diagnostic approaches in bladder cancer and the potential advantages of the above novel strategies [2,15] give cause for hope that some of them may prove valuable and gain acceptance in at least certain clinical situations. That they are important research tools is more certain. ■

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Cost: £165 Full delegate / £100 Trainees and CNSs

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The Royal College of Physicians, London NW1 4LE
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The Royal Marsden Education and Conference Centre, London SW3 6JJ
Cost: £165 Full delegate / £100 Trainees and CNSs

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16 November 2012
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Cost: £165 Full delegate / £100 Trainees and CNSs

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ANNOUNCEMENT

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10th Annual BTOG Conference 2012

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Fri 27th January 2012

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Dublin, Ireland

- Wednesday BTOG Symposium
- Sponsored Satellite Meetings Wednesday
- Thursday & Friday Annual Conference

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British Thoracic Oncology Group (BTOG) is a lung cancer and mesothelioma research group.
The principal aim of BTOG is to encourage the development of clinical and scientific research in all areas of Thoracic Oncology and the provision of a multi-disciplinary educational forum.
All individuals involved in any aspect of lung cancer or mesothelioma research, treatment or care are eligible to become members of the Group.

BTOG Secretariat

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Conference News

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 Patricia McDonnell at Oncology News on T/F: +44 (0)288 289 7023, E: patricia@oncologynews.biz

11th International Society of Geriatric Oncology Meeting

Date: 4-5 November, 2011. **Venue:** Paris, France.

Stuart Lichtman, MD (Scientific chair of the meeting) giving a presentation. Photo ©2011 Xavier Granet.

The conference room with attendance. Photo ©2011 Xavier Granet.

The 11th meeting of the International Society of Geriatric Oncology (SIOG) was held in Paris in November 2011. Founded in the year 2000, the SIOG is dedicated to the education of physicians about the care of the older cancer patient. The Society has a number of activities, in particular task forces which have published important position statements about various aspects of Geriatric Oncology care: chemotherapy, renal dysfunction, surgery, geriatric assessment and others. There is also a National Representatives group whose role is to stimulate interest in Geriatric Oncology in their respective countries. This year's meeting welcomed over 400 attendees from 27 countries with a broad range of specialties. The scientific program was structured so that clinicians with varying interests can benefit and included basic science of aging, review of therapeutic modalities (surgery, radiation therapy), and disease specific sessions (gastrointestinal, breast, ovary, head and neck). There were educational sessions, proffered paper presentations and poster sessions. Earlier meetings of the Society were primarily educational sessions. In contrast the Paris meeting focused more on data from a wide variety of investigator initiated studies. There was a large number of presentations on geriatric assessment instruments utilised in various clinical settings. Topics included evaluations of preoperative assessment, measures including the GFI, G8, studies of the Cancer and Aging Research Group and the CRASH score from the University of South Florida, showing the increasing interest and experience with these various instruments. Presented data showed these assessment tools to be specific for the clinical settings in which they were developed. There may not be a one-fits-all instrument. There will be a need for prospective validation in various clinical settings. However it is clear that great strides have been made since the last meeting in 2009. In view of the small number of trained geriatricians, oncologists will need to familiarise themselves with some of these instruments and bear the responsibility for assessing their patients to aid in treatment decisions. There were also data presented on disease specific clinical trials as well as a number of studies of quality of life, issues of cognitive impairment and symptom burden. A definite highlight of the meeting was the number of excellent proffered papers covering a broad range of topics, demonstrating the increased worldwide interest in geriatric oncology. This 11th meeting in Paris provided an opportunity for interaction among investigators around the globe to stimulate further study.

The Society presented the Calabresi award to Dr Beena Devi in recognition of her contribution to geriatric oncology over these past years, particularly in organising the successful First Asian Congress on Cancer in the Older Patient, held in Kuching in January 2011. Importantly, the Society's next President was elected: Dr. Arti Hurria of the City of Hope. Dr. Hurria is also the Editor-in-Chief of the Journal of Geriatric Oncology.

The current SIOG President is Riccardo Audisio, MD in the United Kingdom, and the Executive Director is Matti Aapro, MD in Switzerland. Stuart M Lichtman, MD (New York) was the Scientific Chair and Etienne Brain, MD (Paris) was the Meeting Chair. The 12th SIOG meeting will be held in Manchester, UK, on October 25-27, 2012. ■

Erratum:

In the Conference Digest section of the November/December 2011, Page 157 Radiotherapy between or during chemotherapy cycles reduces breast cancer recurrence, the first sentence in paragragh three should have read 2.8% in the synchronous arm rather than 28%.

(The five-year local recurrence rates were 2.8% in the synchronous chemoradiation group and 5.1% in the sequential group.)

Measurable steps to reduce the burden of cancer now and for future generations agreed at the 2011 World Cancer Leaders' Summit

Date: 18 November, 2011. **Venue:** Dublin, Ireland.

On 18 November 2011, 240 representatives of governments, the World Health Organisation (WHO) and the World Economic Forum, plus civil and corporate leaders from over 60 countries, met at the World Cancer Leaders' Summit (WCLS) in Dublin to publically agree the actions incumbent on governments and societies to halt the spiralling global cancer epidemic.

Organised by the Union for International Cancer Control (UICC) and the Irish Cancer Society, the two-day event was the first opportunity since the UN High-Level Meeting on non-communicable diseases (NCDs) for civil society, health, government, philanthropic and corporate leaders from around the world to agree strategies and actions to convince governments to commit to specific time-bound targets that address the global burden of cancer. A key focus of the meeting discussions was the need to create commitment to measurable actions in priority areas – including pain control/palliative care, cancer registries, public-private partnerships, cancer control in the developing world and best practice in disease control public policy – with the ultimate aim of reducing premature deaths from cancer and other NCDs by 25% by 2025.

"With an increasing number of cancer cases being diagnosed across the world (particularly in low- and middle-income countries), due to a large extent to preventable factors, the global incidence of cancer is projected to rise from 12.7 million in 2008 to 21.4 million by 2030," stated speaker Andreas Ullrich MD MPH, Medical Officer Cancer Control, Department Chronic Diseases and Health Promotion, WHO Headquarters Geneva. "The world must act now to reduce the human suffering and economic impact of this disease."

A key outcome of the WCLS was the ratification of the Dublin Resolution. This statement of intent, signed onsite by many delegates, spells out the measurable actions required by governments and societies to help achieve the shared ambition of reducing the social and economic burden of cancer for future generations. These are:

- Developing time-bound indicators by 2012 that address the increasing cancer epidemic
- Promoting the inclusion of cancer-related targets in the post-2015 Millennium Development Goals
- Promoting local policies and approaches that will strengthen and facilitate multisectoral action against the disease
- Promoting sustainable and adequate resourcing in the areas of cancer prevention, early detection, treatment and care.

"It is unacceptable that millions of people worldwide still suffer unnecessarily and die prematurely from cancer," commented Cary Adams, UICC Chief Executive Officer. "To give the world the best chance of dramatically reducing the cancer epidemic, UICC urges world leaders to support the commitments of the Dublin Resolution by promoting sustainable resourcing and measurable targets for cancer in their countries." ■

For further information visit W: www.uicc.org

Marie Curie Annual Palliative Care Research Conference

The challenge of symptom control in advanced progressive disease: what can we do?

Date: 23 March, 2012. **Venue:** London, UK. **PREVIEW**

We know from clinical practice that people with advanced, progressive disease who are approaching the end of life experience numerous distressing symptoms that are often difficult to control. The burden is similar in both cancer and non-cancer diagnoses, although in many non-cancer diagnoses, such as dementia, symptoms are poorly recognised by clinicians.

For patients, research into how we can identify and attempt to manage these symptoms and their consequences is a high priority. Such research includes understanding how and why symptoms occur, which treatments might be most effective for which patients, how these treatments can be put into practice, and what the long-term effects on patients and families might be.

At our Marie Curie Annual Palliative Care Research Conference this year, we shall update our thinking in these areas. We shall hear talks from expert researchers working on a range of common symptoms, including pain – the one which many of us fear the most.

There will be more free research papers than ever before as well as 20 posters – all chosen in open competition. We will end the day with an interactive session in which we explore issues of how we might put new knowledge into practice.

Invited Speakers:

Professor Mike Bennett, St Gemma's Professor of Palliative Medicine, Leeds Institute of Health Sciences School of Medicine, University of Leeds

Dr Joy Ross, Consultant in Palliative Medicine, Royal Marsden and Royal Brompton Palliative Care Service Honorary Clinical Senior Lecturer, Imperial College London

Professor Frances Mair, Professor of Primary Care Research and Head of General Practice and Primary Care, Institute of Health and Wellbeing, University of Glasgow

Professor Alex Molassiotis, Professor and Chair of Cancer and Supportive Care, University of Manchester

Joanna Eley, NCRI Consumer Liaison Group Representative. ■

For further information visit:
W: www.rsm.ac.uk/academ/plc04.php

News update

Latest developments on products and services from the industry. To have your news included contact Patricia McDonnell on patricia@oncologynews.biz or T/F: + 44 (0)288 289 7023.

Swedish University Hospital orders four of Varian's TrueBeam™ radiotherapy systems

Varian Medical Systems has been awarded a contract to supply four TrueBeam™ treatment systems to Lund University Hospital in Sweden, one of the country's largest radiotherapy departments. The order is aimed at cutting treatment waiting lists in the Skåne region of Sweden and includes an option to acquire two further TrueBeam™ systems in 2014.

The TrueBeam™ devices will replace treatment machines from a rival manufacturer and Varian's ARIA software suite is replacing the incumbent software, as Lund University Hospital and its partner site at Malmö University – which combined under the banner Skåne University Hospital last year – switch to an integrated, single-vendor environment.

"We are looking to offer fast and advanced radiotherapy treatments at Lund and Varian was selected because it fulfils our quality demands," says lead radiation oncologist Dr Thomas Björk-Eriksson. "We need machines that can deliver very conformal radiotherapy in a fast and safe way, enabling us to offer advanced techniques such as RapidArc® volumetric radiotherapy and stereotactic radiosurgery.

"This region currently has waiting lists for radiotherapy of four to eight weeks and we want to reduce that to less than two weeks," adds Dr Björk-Eriksson. "We believe our new equipment and software will enable us to work towards that target."

For further information contact:
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Optimal chemo-radiotherapy approaches in NSCLC – A proposal for a national trial

On the 13th of October a meeting was held to develop clinical trial proposals that aim to standardise chemo-radiotherapy in the UK. A recent Cochrane review[1] of radical chemo-radiotherapy demonstrated the benefit of a concurrent approach over a sequential treatment or radiotherapy alone. This is reflected in recent NICE guidelines, but an assessment of radiotherapy services offered in the UK showed that almost 40% of centres remain unable to deliver combined modality treatment.

The meeting was attended by a number of Consultant Oncologists, Radiographers, Statisticians, and included representation from Cancer Research UK (CR-UK) and patient groups. It was agreed that treatment recommendations should address all those patients with stage III disease receiving curative, non-surgical, treatment; those suitable for first definitive concurrent chemo-radiotherapy and those unsuitable, for reasons including performance status and pre-existing medical conditions.

A concurrent study would compare accelerated hypofractionated chemo-radiotherapy with conventional chemo-radiotherapy. For those patients unsuitable for concurrent treatment there are three CR-UK phase I/II trials currently recruiting to define a personal approach to radiotherapy dosing (CHART-ED, IDEAL and iSTART). Continued recruitment to these is encouraged and future studies in this population of patients will randomise the preferred/best approaches.

A consensus was agreed for further protocol development to proceed and the group will meet again at January's British Thoracic Oncology Group meeting to take a proposal forward to CR-UK.

This meeting was supported with an unrestricted medical grant from Pierre Fabre. For further information please contact:
E: nikki.roebuck@pierre-fabre.com

Reference
1. O'Rourke N et al. *Concurrent chemoradiotherapy in non-small cell lung cancer.* Cochrane Database Syst Rev. 2010 Jun 16;(6):CD002140.

CureVac presents results of a Phase I/IIa trial in NSCLC with CV9201

CureVac, the mRNA vaccine company, recently presented the results of a Phase I/IIa trial in non-small cell lung cancer (NSCLC) with CV9201, an mRNA-based cancer vaccine, in patients with NSCLC stage IIIB/IV after first-line chemo-radiotherapy or chemotherapy, respectively. The trial strived to assess safety and toxicity of CV9201 as well as its ability to induce antigen-specific humoral and cellular immune responses in cancer patients. The results suggest that CV9201 is safe, well tolerated and biologically active. The trial evaluated a five dose regime of CV9201 delivered via intradermal injection in 46 patients.

The trial with CV9201 was the first to test an immunotherapy based on CureVac´s RNActive® vaccination technology in patients after heavy pre-treatment with chemotherapy. 65% of the phase IIa study patients responded to at least one antigen out of the five antigens in CV9201. "Importantly, CureVac's therapeutic mRNA vaccine CV9201 induces responses against multiple antigens in two thirds of immunologically responding patients. Moreover, we see profound B-cell activation in 61% of the patients. This makes an overall antigen-specific or B-cell response of 84%. We also see immune responses against all included antigens.

CureVac´s RNActive® tumour immunotherapy approach is independent of the HLA subtype. CV9201 is one candidate in CureVac's pipeline of RNActive®-derived molecules for the active immunotherapy of cancer. The vaccine comprises mRNA molecules encoding five different antigens of which three are cancer testis antigens.

All in all, these data are extremely encouraging and confirm our previous results in prostate cancer," said Dr. Kajo Kallen, CSO and CMO of CureVac.

For more information visit: W: www.curevac.com

Modular upright research microscopes for bioscience and medical research

The Nikon evolution in upright biological microscopes has advanced with the new Eclipse Ni series. Using core technology from Nikon's renowned Eclipse Ti inverted research microscope, the Eclipse Ni series offers multi-mode system expandability to meet the imaging needs of bioscience and medical research on one platform. The new Ni range also provides superior optical performance with new CFI Plan Apochromat Lambda series objectives, and the flexibility of assisted observation by motorisation. The range comprises the fully motorised Eclipse Ni-E flagship model with focusing nosepiece or focusing stage options, and the manual Eclipse

Ni-U with motorisation upgrade capability.

Nikon's highly acclaimed proprietary stratum structure in the Ni series opens up a vast range of imaging possibilities that can be upgraded at any time. Both models support research into the reactions and changes of stimulated cells with a newly developed photoactivation unit, a first for upright microscopes. The Eclipse Ni-E is also configurable for multiphoton imaging, as well as offering the option of fixed-stage configurations to meet the demands of experiments such as *in vivo* imaging for cardio vascular and neuroscience research applications.

For further information contact:
Nikon Instruments: T: +44 (0)208 247 1718,
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ICH selects Leica Microsystems to provide automated IHC platforms

Imperial College Healthcare NHS Trust has one of the largest immunohistochemistry / in situ hybridisation (IHC / ISH) workloads in the UK, performing almost 120,000 IHC slides a year. The Trust has selected Leica Microsystems' BOND platform to provide advanced IHC and ISH staining capabilities for cellular pathology services at its Hammersmith, Charing Cross and St Mary's Hospital sites. These hospitals are integrated with the Faculty of Medicine at Imperial College London, rated in 2011 as a top 10 global university by Times Higher Education in conjunction with Thomson Reuters.

The Trust has recently installed a total of 10 new Leica BOND systems, offering increased throughput and improved staining consistency for a wide range of assays. Donna Horncastle, Laboratory Manager for Cellular Pathology at Hammersmith Hospital, explained, "Cellular pathology services within the Trust are split across three separate laboratories, with each site covering a range of specialties. In order to standardise our practices we wanted to switch to fully automated immunostaining for both routine and research IHC and ISH. Following a comprehensive tender process, Leica Biosystems were able to offer the best solution for our needs, combining good staining quality with high throughput."

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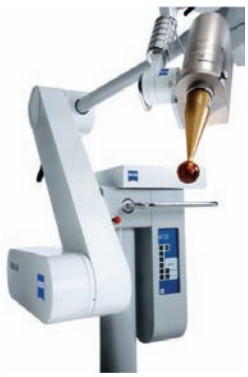
Zeiss Intrabeam®

Carl Zeiss (CZ) would like to announce the appointment of Alex Kypriotis as sales and business development manager for the Intrabeam® radiotherapy product portfolio. Alex has been appointed specifically to look after the Intrabeam® business of CZ in the UK and Ireland since the interest for this product has grown exponentially within the last two business years.



This radiotherapy device which is used for intra-operative radiotherapy (IORT) in breast cancer is a paradigm shift compared to conventional treatment technology and has a proven safety and efficacy profile in clinical practice since 1998 within the 'TARGIT' trial and beyond. Since the recently published article in *The Lancet* and associated data as well as other papers demonstrating quality of life and non-inferiority, new hospital departments have implemented this innovative technology and key opinion leaders are taking notice.

Alex will be supporting the current user base which has grown by 14% within the last year and using his extensive commercial and clinical background in radiotherapy to develop further partners within IORT.

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Wellington Hospital is first in southern hemisphere to offer patients TrueBeam™ treatments

Clinicians at one of New Zealand's leading hospitals have delivered more than 300 radiotherapy treatments using a newly-installed TrueBeam™ device in the first month of its implementation. The TrueBeam™ system from Varian Medical Systems adds to Wellington Hospital's radiotherapy capabilities and enables fast, precise and efficient treatments.

The first patient in the country – and the southern hemisphere – to be treated using the TrueBeam™ device was an 18-year-old man with Hodgkin's disease. "He commented on the speed with which the treatment was delivered and was enthusiastic to be our first patient treated on TrueBeam™," says Jennifer de Ridder, radiation therapist team leader at Wellington Hospital. "Many of our patients have commented on the speed of their treatments, which is a significant factor for those who are immobilised during treatment."

To manage treatment waiting times in New Zealand, the government recently introduced a target that all patients should commence radiotherapy within four weeks of a decision to treat. "We usually meet this target but need to be more efficient to continue meeting it in

future," says Carole Johnson, clinical leader of radiation oncology. "So more advanced treatment techniques must be incorporated without making treatment slots longer and without impacting our ability to meet this waiting time target. TrueBeam™ helps us to achieve this."

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The London Clinic launches new Advanced Therapies Centre

The Advanced Therapies Centre provides one of the first clinical trials programmes in the independent healthcare sector and will focus on Phase II and III clinical trials, offering patients access to the latest advances in treatments.

Housed in The London Clinic's new £90 million cancer centre, the first trials being undertaken focus on oncology including studies of immunotherapy agents in pancreatic and colorectal melanoma, amongst others. Further proposed studies include a comparison of the superiority of stereotactic radiosurgery with CyberKnife for cancers that have metastasised.

Alistair Gifford-Moore, Clinical Trials Manager states "Clinical trials are vitally important to

constantly improve the care of those with cancer. The new Advanced Therapies Centre is an exciting step forward for clinical research at the Clinic."

The programmes benefits include a rapid study set up time in 42 days, rapid patient recruitment with access via consultants' private practices and the Named Patient Programme allows equal access for private patients to unlicensed medication and off-label treatment in a controlled environment.

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Nucletron's VCMC applicator now in clinical use at Nottingham

Nottingham University Hospital recently purchased Nucletron's* Vaginal CT/MR Multi Channel (VCMC) Applicator and has now commenced clinical treatment using the new equipment. Initial feedback confirmed that treatment procedures are easier to perform with the applicator compared to current methods of delivery and that it is non-traumatic for patients. Dr Stephen Chan Clinical Oncologist comments, "Radiotherapy is the only curative treatment for the group of patients with cancer of the vagina. In the past we have used interstitial needles. This means the patient has a general anaesthetic for the insertion and remains immobilised in bed for three days. With the less invasive VCMC applicator we were able to treat the patient without an anaesthetic and on an outpatient basis. This was much more convenient for the patient and eliminated the trauma of needle insertion. It also removed the cost associated with theatre, anaesthetics and in-patient stays."

For further information visit:
W: www.nucletron.com
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*Nucletron, an Elekta company

Nucletron's Vaginal CT/MR Multi Channel Applicator (VCMC).

Centre Val d'Aurelle first hospital in France to deliver advanced radiotherapy treatments using TrueBeam™

A 19-year-old brain tumour patient has become the first person in France to be treated using the highly advanced TrueBeam™ radiotherapy treatment system from Varian Medical Systems. The male patient's cerebral glioblastoma was treated quickly and efficiently at the Cancer Research Center of Languedoc-Roussillon at the Centre Val d'Aurelle, Montpellier. Following this initial treatment, dozens more patients have been treated using the newly-deployed device, one of three acquired by the hospital.

"We believe that the system's dose delivery speed and its unique ability to image the patient during the treatment will bring considerable benefits for our patients," says Professor Jean-Bernard Dubois, head of radiotherapy. "With TrueBeam™ we are able to image the tumour during the treatment and adapt the treatment delivery in 'real-time', which helps to better target the tumour and limit damage to surrounding healthy organs."

Dr. Pascal Fenoglietto, head of research of the hospital's physics department, said the TrueBeam™, which is now treating 20 patients a day, can deliver dose up to six times more quickly than other treatment devices, enabling much greater throughput at the busy hospital.

"We considered other systems but it was clear that TrueBeam™ can achieve the same treatment quality in a dramatically shorter time," he said.

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Hospital St John and St Elizabeth purchase Intrabeam®

The Hospital of St John and St Elizabeth is delighted to be one of the first private hospitals in the UK to have installed Intrabeam® by Zeiss for use in treatment of breast cancer. Intraoperative radiotherapy (IORT) involves giving a high dose of radiation therapy during surgery, precisely targeting the affected area with minimal exposure to the surrounding tissue during the lumpectomy procedure. This treatment can replace conventional postoperative external beam radiotherapy (EBRT) or is used in conjunction, with a reduced frequency of EBRT treatments.

Early results show that one dose of IORT has been proven to be as effective as 30-35 standard EBRT treatments by the large multicentre 'TARGIT' Trial.

Mr Mo Keshtgar, an internationally renowned Breast Surgeon who heads the team of consultants in The Breast Unit has helped to pioneer the use of IORT in the UK and is a world leading expert in breast cancer care. The Bupa registered Breast Unit is based at the unique charitable Hospital of St John and St Elizabeth in central London.

For further information, please visit the website: www.thebreastunit.org.uk

brainstrust charity awarded Information Standard Accreditation by the Department of Health

brainstrust's commitment to excellent patient information has been granted an official stamp of approval by the Department of Health which has awarded the charity with the Information Standard. This makes brainstrust the first dedicated brain tumour charity in the UK with this accreditation – the mark of high quality information. The purpose of this DoH sponsored scheme is to give members of the public an easy way to identify trustworthy health information on the Internet or in print.

With over 170,000 charities in the UK alone, brainstrust joins an elite band of just 126 to hold this accreditation.

Ingela Oberg, a specialist nurse at Cambridge University Hospitals Foundation Trust, finished with, "As a neuro oncology specialist nurse I am delighted to know that a UK brain tumour charity has achieved the highest standard of information accreditation. For the patients it means they have immediate access to trustworthy, evidence based information which is not only informative, but also concise as well as regularly updated. It means a lot to us as specialist nurses up and down the country knowing that we can signpost our patients and their families and carers to information, knowing they do not need to filter through any un-vetted information that may cause them undue stress and anxiety."

For further information visit W: www.theinformationstandard.org, or www.brainstrust.org.uk

Improving patient care takes more than just electronic prescribing

Elekta is the world leader in providing advanced clinical solutions for radiosurgery and radiation therapy, giving unmatched capability to aggressively treat tumours and functional targets with ultra-high precision. Elekta's sophisticated workflow enhancing software and treatment planning systems for Radiation Oncology and Medical Oncology provide state of the art tools and techniques across the spectrum of cancer care.

Leveraging more than 20 years of leadership and expertise, Elekta's MOSAIQ® Oncology Information System continues to set the standard for comprehensive patient charting, connectivity and usability across Radiation Oncology and Medical Oncology disciplines in a single system.

More than 1,400 global customers count on Elekta software to help them provide the safest and most efficient treatments in the fight against cancer.

From its multiple safety features, comprehensive electronic prescribing and dispensing, advanced scheduling, documentation and reporting capabilities, MOSAIQ is the tool of choice to effectively manage both Radiation therapy and Chemotherapy in cutting-edge treatment centres from a single database.

For further information contact: Patrick Greally, Elekta Limited, T: +44 (1293) 654 462, E: Patrick.Greally@elekta.com

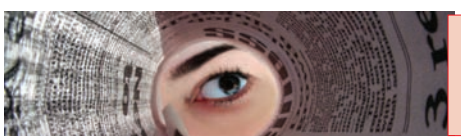
World-renowned cancer centre to become all-TrueBeam™ clinic in battle against cancer

One of Europe's leading cancer centres will be offering radiotherapy and radiosurgery treatments using fast and precise TrueBeam™ systems from Varian Medical Systems. The Maastro Clinic has acquired three TrueBeam™ systems for its main site in Maastricht and a satellite site in nearby Venlo as part of a project to replace all its equipment and software from an incumbent supplier.

"This will make a big improvement to the quality of cancer treatments for patients in this region and we are delighted to be able to introduce TrueBeam™ treatments in the Limburg area," says Maria Jacobs, managing director of the Maastro Clinic. "We intend to become the first cancer center in the world entirely equipped with TrueBeam™ systems."

Two further systems have been ordered for satellite site Venlo where installation is planned for 2012. Maastro has signed a contract for three additional TrueBeam™ devices which are intended to be installed in stages at the main clinic. The hospital has also ordered a full suite of Varian software for treatment planning and oncology information management.

For further information contact: Neil Madle, Varian Medical Systems, T: +44 (0)7786 526068, E: neil.madle@varian.com



To have your news item included in this section contact
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CureVac, Sanofi Pasteur and In-Cell-Art collaborate on a $33.1m project

CureVac GmbH recently announced the signing of several agreements with Sanofi Pasteur SA, the vaccines division of Sanofi. Under these agreements, CureVac and Sanofi Pasteur will further develop and apply CureVac's proprietary RNActive® technology platform to the development of vaccines against several infectious diseases and several tumours.

A research proposal with total funding of $33.1 million involving a collaboration among CureVac, Sanofi Pasteur (including Sanofi Pasteur VaxDesign Corp.) and In-Cell-Art SAS, a French biotech company contributing its nanoparticle technology, has been selected by DARPA, the Defense Advanced Research Projects Agency (an agency of the United States Department of Defense). In this four-year project, CureVac and the other parties to the collaboration will further advance key aspects of CureVac's RNActive® technology platform and will evaluate several vaccine candidates in a number of relevant disease models.

CureVac´s RNActive® tumour immunotherapy approach is independent of the HLA subtype. CV9201 is one candidate in CureVac's pipeline of RNActive®-derived molecules for the active immunotherapy of cancer. The vaccine comprises mRNA molecules encoding five different antigens of which three are cancer testis antigens.

For more information visit:
W: www.curevac.com

Zeiss Intrabeam® installed at The Princess Grace Hospital

The renowned pioneer of Inter Operative Radiotherapy, (IORT), breast surgeon Mr Jayant Vaidya, has joined the breast care team at The Princess Grace Hospital in central London.

Mr Vaidya co-developed IORT – a process whereby a single dose of radiotherapy is delivered directly into the breast following the removal of a tumour before the completion of the operation – in the late 1990s together with a distinguished team of cancer specialists, at University College Hospital London.

IORT avoids women having repetitive radiotherapy sessions over a three to six weeks period, some weeks after their operation. This novel approach, uses an Intrabeam® radiotherapy machine which was designed by Mr Vaidya and the UCH team. The procedure is called TARGeted Intra-operative radiotherapy (TARGIT). This procedure has been on trial for over a decade by breast cancer teams around the world with extremely favourable results recently published in *The Lancet*.

The Princess Grace hospital is one of the first private hospitals in the UK to install the Intrabeam® radiotherapy device with service commencement expected in early 2012.

For further information visit:
W: www.Zeiss.co.uk

OSL expands

Oncology Systems Limited is starting 2012 on a high with two new distribution contracts. OSL has signed a five year distribution deal with US-based fiducial marker manufacturer Cortex, the people behind the original ACCULOC markers; and secured a new distributor for its own ImSimQA software in the Netherlands, Medsuro Medical Equipment.

The Cortex contract will see OSL sell the company's advanced implanted marker line in the UK and Ireland. Stuart Baldwin, OSL's sales director said: "This revolutionary new range of advanced markers complements our existing offerings and gives us the flexibility to offer a complete solution for all treatment sites and imaging modalities, including new breast markers and markers that show up equally well in both CT and MR."

ImSimQA's most advanced functionality to date was launched on 19 December 2011, with more extensive QA tools for testing techniques such as deformable image registration and atlas-based auto contouring that are now essential for IMRT, ART, IGRT and SBRT. Dean Willems, OSL product specialist believes that Medsuro Medical Equipment is the perfect partner for the distribution of the software. He said: "Medsuro has vast experience in radiotherapy and we look forward to ImSimQA being in use across the Netherlands during 2012."

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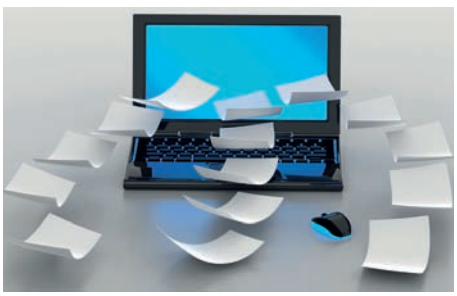
...a cancer registry system with automated case finding



With METRIQ®, it's reality.

With METRIQ® features such as PathConnect™ and MOSAIQ® Connect, reports are electronically received and reviewed for inclusion in the METRIQ cancer registry database. With METRIQ, recently diagnosed patients with cancer and follow-up information are automatically uploaded into your cancer registry system. The case finding import is uploaded at the touch of a button, decreasing errors, improving workflow and saving time.

LADMTQ110908 v1.0

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